IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIODELIVERY SCIENCES INTERNATIONAL, INC. and ARIUS TWO, INC.,	)	
Plaintiffs,	)	C.A. No. 18-1395 (CFC) (CJB)
v.	)	
ALVOGEN PB RESEARCH & DEVELOPMENT LLC, ALVOGEN MALTA OPERATIONS LTD., ALVOGEN PINE BROOK LLC, ALVOGEN, INC., and ALVOGEN GROUP, INC.,	)	
Defendants.	)	

PLAINTIFFS' RESPONSES TO DEFENDANTS' PROPOSED FINDINGS OF FACT AND SUPPLEMENTAL FINDINGS

Plaintiffs, pursuant to the Court's oral order (Tr.956:16-24), have responded to each of Defendants' 275 proposed findings of fact. Plaintiffs' responses to Defendants' Findings are called "DFF." Plaintiff has also supplemented its responses with its own proposed finding of fact, "PFF" as appropriate.

Defendants Finding No. 1. The Tapolsky patents are generally directed to a bioerodable mucoadhesive ("BEMA") device that includes (1) a polymeric diffusion environment (or "mucoadhesive layer") containing the drug, at least one film-forming water-erodible adhesive polymer and at least one bioadhesive polymer, and (2) a backing layer (or barrier layer) to provide a "unidirectional gradient" of the drug toward the mucosal surface and prevent the drug from being swallowed. (See generally DTX-173, see also Tr. 106:17-109:21.)

DFF1. Denied. Defendants do not define what they mean by "Taposkly patents." The only "Tapolsky" reference admitted into evidence and referred to at trial was US2005/0147658 A1 ("Tapolsky-2005"), which is DTX-173.

Tapolsky-2005 does not describe a "BEMA device" as that phrase is used in the patents-in-suit. Tapolsky-2005 does not use the term "BEMA," nor the expression it stands for—"Bioerodable MucoAdhesive Layer. DTX-0173. "BEMA" is the trademarked name of the technology developed by BDSI that is used to develop their transmucosal products. DTX-019-0007.

Tapolsky describes a two-layer device. This device, however, does not contain a polymeric diffusion environment, as understood in the patents-in-suit. The '866 patent states that the "novel polymeric diffusion environment" enhances the "absolute bioavailability of the medicament contained therein," and also provides "rapid onset." JTX-0001, col.4:31-37; (Tr.584:18-585:1). The flux of the medicament from the polymeric diffusion environment into the mucosa can be enhanced by taking into the account the pH and the ionic nature of the polymers. (JTX-0001, col.6:16-24.) It was the inventors of the patents-in-suit that developed the polymeric diffusion environment buffered to a particular pH range that resulted in "tremendous" and "unexpected" bioavailability for buprenorphine. (Tr.750:16-23; 802:21-24.)

Tapolsky-2005 only states that a film-forming water erodible adhesive polymer and a bioadhesive polymer "may" be used. (DTX-173, ¶31.) Tapolsky-2005 does not teach a *two*-layered device with unidirectional delivery. Taopilsky-2005 describes a two layered device that "provides *some* directional release." (DTX-173 at ¶ 58.) To obtain specific unidirectional delivery, Tapolsky-2005 describes needing a third layer. (*Id.)*

PFF1. Tapolsky-2005 does not teach a polymeric diffusion environment buffered to a particular pH (Tr.262:4-9, 652:3-5), as recited in the asserted claims of the patents-in suit.

Defendants Finding No. 2. The Tapolsky patents are platform technology useful for many categories of drugs, including opioids. For example, Tapolsky identifies butorphanol as an exemplary opioid for use in the patented BEMA device. (DTX-173 at [0053], *see also* Tr. 112:16-23.)

DFF2. Denied. *See* Resp. DFF1; PFF1-6.

PFF2. Tapolsky-2005 includes butorphanol in a laundry list of more than 200 pharmaceutical compounds, and nowhere indicates that butorphanol is "as an exemplary opioid." The term "opioid" is not even used in Tapolsky-2005. *See* DTX-173; (Tr.261:16-262:3).

PFF3. In the paragraph mentioning butorphanol, Tapolsky-2005 lists more than 70 other compounds and calls these compounds "[o]ther pharmaceuticals." (Tr.261:20-262:3); DTX-173, ¶53.

PFF4. Tapolsky-2005 identifies numerous classes of pharmaceutical compounds suitable for its device (DTX-173, ¶¶48-51), but does not identify opioids.

PFF5. A POSA could not predict how buprenorphine would behave in the claimed devices based on the chemical structure of butorphanol. (Tr.744:22-745:20, 746:8-20, 254:17-255:6, 256:13-15, 278:20-22.)

PFF6. "Different active agents may behave differently within the delivery platform of Tapolsky-2005 because their physical and chemical properties are likely to differ." (Tr.260:5-261:3.)

Defendants Finding No. 3. The '866 and '843 patents generally claim a Tapolsky BEMA device containing buprenorphine, wherein the polymeric diffusion environment is buffered to a pH that is optimal for the dissolution, ionization and absorption of buprenorphine. (*See generally* JTX-001, JTX-002, *see also* Tr. 200:21-201:5.)

DFF3. Denied. *See* Resp. DFF1; *see* PFF1-14.

PFF7. A POSA would not have been able to predict how different chemical compounds would behave in the devices of Tapolsky-2005 based on Tapolsky's experimentation in dogs with testosterone and albuterol sulfate. DTX 173-0015, ¶131; (Tr.260:5-261:3, 256:9-15, 422:19-23, 423:3-11, 742:1-744:20, 808:16-809:6).

PFF8. Tapolsky-2005 does not describe working with buprenorphine, the administration of buprenorphine to a subject, the enhanced uptake

of buprenorphine, the rapid and efficient delivery of buprenorphine, the polymeric diffusion environment developed by the inventors that results in enhanced bioavailability, or buffering that environment to a pH between 4 and 6, or between 4.5 and 5.0, or between 4 and 7.5. (Tr.262:4-9, 421:17-19, 621:23-624:3, 652:3-7; 742:20-743:1;) DTX-173; JTX-365-0004; PFF12. These elements are claimed by the '866 and '843 patents. JTX-0001-0019; JTX-0002-0021.

PFF9. Tapolsky-2005 does not describe an effective plasma concentration of buprenorphine for at least four hours or a first quantifiable plasma concentration of buprenorphine at 45 minutes, as recited in claims 4 and 5 of the '866 patent. JTX-0001-0019; (Tr.262:13-15, 810:1-20.) A POSA would understand from Tapolsky-2005 that the first quantifiable plasma measurement of albuterol sulfate was at time zero. (Tr.422:19-23, 808:16-809:25.) Tapolsky-2005 does not disclose what constitutes an effective plasma concentration of albuterol sulfate. (Tr.422:24-423:2, 810:9-20.)

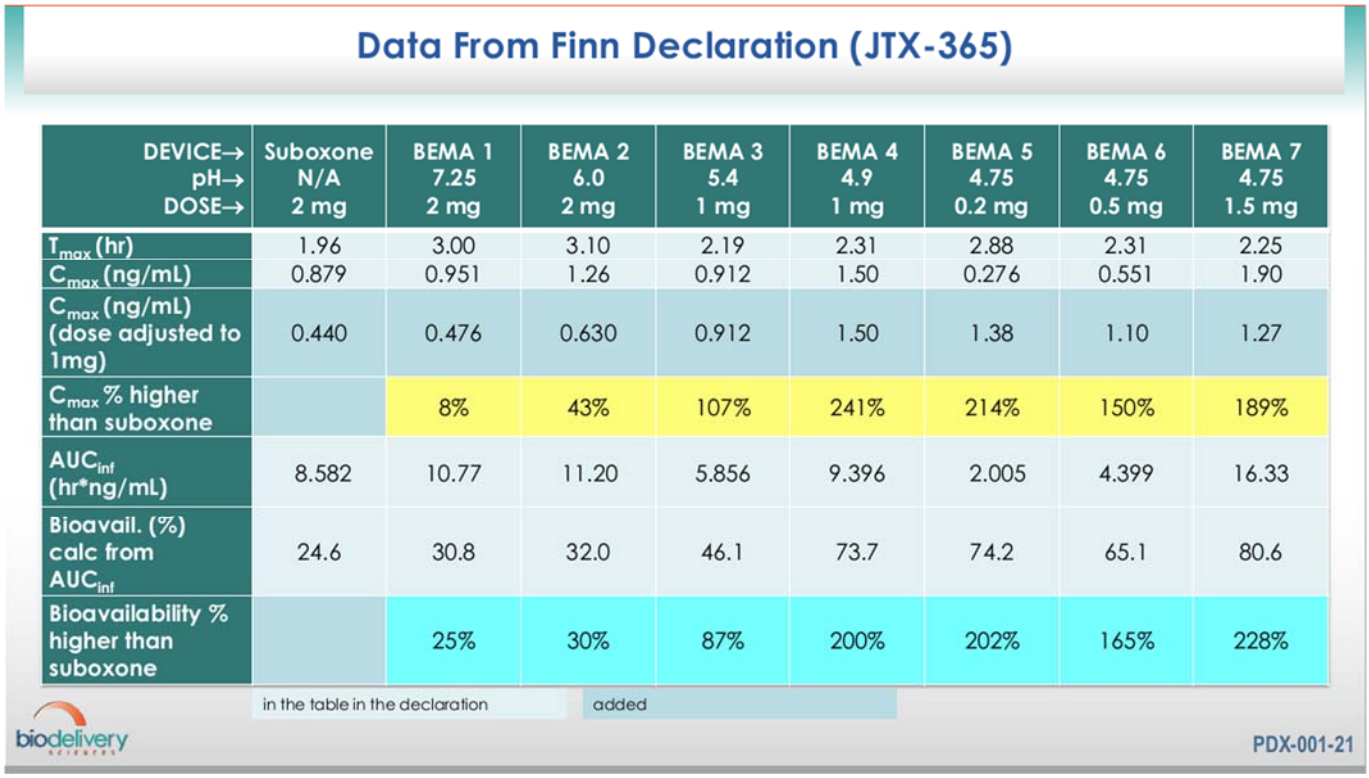
PFF10. The inventors of the patents in suit experimented with the polymers of the layers of the device to create a series of different formulations containing different combinations of polymers in certain

ratios (P1 through F24) through the course of many years. (DTX 370-0026-0043).

PFF11. As stated by Dr. Vasisht, an inventor of the '866 and '843 patents: "Of course, the bilayer product that was developed that enabled the mucoadhesive layer that comprises the buprenorphine and a polymeric diffusion environment, that was something that I created." Tr.750:17-20.

PFF12. The invention claimed in the '866 and '843 patents is directed to the enhanced uptake of buprenorphine, as measured by bioavailability and maximum plasma concentration. *See e.g.,* JTX-001-0001, 0006, 0007, 0018, claim 1. The pH ranges described and claimed in the '866 and '843 patents result in such enhanced uptake. JTX-0365-0004; Tr.648:6-650:21, 799:9-804:1, 941:3-945:19; JTX-365-0003-04; JTX-352-0007; JTX-353-2009, 1123, 2004; JTX-0349-0042-43.

PFF12.1 Data from the underlying buprenorphine studies (BUP-101, BUP-110, and BUP-115) were presented to the PTO during the prosecution of the '866 patent. JTX-365-0004; JTX-352-0007; JTX-353-2009, 1123, 2004; JTX-0349-0042-43.



Data From Finn Declaration (JTX-365)

DEVICE→ pH→ DOSE→	Suboxone N/A 2 mg	BEMA 1 7.25 2 mg	BEMA 2 6.0 2 mg	BEMA 3 5.4 1 mg	BEMA 4 4.9 1 mg	BEMA 5 4.75 0.2 mg	BEMA 6 4.75 0.5 mg	BEMA 7 4.75 1.5 mg
T_{max} (hr)	1.96	3.00	3.10	2.19	2.31	2.88	2.31	2.25
C_{max} (ng/mL)	0.879	0.951	1.26	0.912	1.50	0.276	0.551	1.90
C_{max} (ng/mL) (dose adjusted to 1mg)	0.440	0.476	0.630	0.912	1.50	1.38	1.10	1.27
C_{max} % higher than suboxone		8%	43%	107%	241%	214%	150%	189%
AUC_{inf} (hr*ng/mL)	8.582	10.77	11.20	5.856	9.396	2.005	4.399	16.33
Bioavail. (%) calc from AUC_{inf}	24.6	30.8	32.0	46.1	73.7	74.2	65.1	80.6
Bioavailability % higher than suboxone		25%	30%	87%	200%	202%	165%	228%

in the table in the declaration added

biodelivery sciences

PDX-001-21

PFF12.2 Based on the strong trend when plotting the BEMA 1-7 data in the Finn declaration, a POSA would conclude that C_{max} and bioavailability increased as pH of the BEMA devices decreased. Tr.438:25-439:6, 649:7-24, 802:25-803:18, 941:9-942:7.

PFF12.3 As an example, the Cmax for BEMA 2 was 43% higher than the Cmax for Suboxone. Tr.943:8-944:2.

PFF12.4 A POSA would not have expected the increases in Cmax and bioavailability data for the BEMA 1-7 devices as the

pH of the BEMA devices decreases. Tr.650:9-21, 800:20-804:1.

PFF12.5 A linear regression comparing bioavailability and Cmax data to pH for BEMA 1-7 shows that the trend in increasing bioavailability and Cmax as pH decreases is statistically significant and an appropriate interpretation of the data. Tr.437:22-439:22, 441:15-23, 945:5-945:19.

PFF13. The claims of '866 and '843 patents recite a bi-layer device, containing a mucoadhesive polymeric diffusion layer and a barrier (referred to often as a "backing layer") that has "enhanced direct transmucosal delivery" of buprenorphine. Buprenorphine is disposed in the mucoadhesive polymeric diffusion layer (also called "polymeric diffusion environment"). (Tr.584:18-585:1.) The two layers provide a unidirectional gradient so that buprenorphine is delivered from the mucoadhesive layer to the mucosal surface. (Tr.585:2-9, 585:5-586:20.) Both layers in the claimed invention are bioerodible. (Tr.585:19-586:4.)

PFF14. The '866 and '843 patents describe that the backing layer is significantly thicker than the mucoadhesive layer, so that the device maintains a unidirectional flow of buprenorphine from the

mucoadhesive layer to the mucosal membrane, such that it is not washed away by saliva. (Tr.592:8-593:25); JTX-0001, col.17:44-57.

Defendants Finding No. 4. The '539 patent is generally directed to a Tapolsky BEMA device disclosed in Vasisht I, wherein the backing layer is buffered to a pH of 4.0 to 4.8. (*See generally* JTX-003, *see also* Tr. 209:18-210:3.)

DFF4. Denied. The '539 patent does not describe a "Tapolsky BEMA device." *See* Resp. DFF1; PFF1-6, 9-10, 12.

Defendants Finding No. 5. A POSA would have a bachelor's degree in pharmaceutical sciences, chemistry or related field, plus three to five years of relevant experience in developing transmucosal dosage forms. Alternatively, a POSA would have a Ph.D. in one of those fields and less practical experience. (Tr. 87:10-25.)

DFF5. Denied. While Plaintiffs disagree with Defendants' definition, this issue is moot as Plaintiffs' counsel explained that the non-obviousness issue would be the same if Defendants' definition was accepted. (Tr.88:1-16.)

Defendants Finding No. 6. At trial, BDSI did not object to this description of a POSA, and, Dr. Robert Williams testified that his opinions on behalf of BDSI would not change in view of this definition of a POSA. (Tr. 88:1-88:14, 721:22-722:4.)

DFF6. Denied. *See* Resp. DFF5. Further, there is no citation to Dr. Williams' testimony provided in the finding.

Defendants Finding No. 7. Buprenorphine, discovered in 1966, is an opioid analgesic known to treat acute and chronic pain. (DTX-165-0001-0003, 0008-0009; JTX-471-0003; Tr. 96:15-25, 97:19-98:1, 98:3-22.)

DFF7. Denied. *See* PFF15-17.

PFF15. As of 2006, in the United States, buprenorphine was not approved for the treatment of chronic pain. DTX-165-0001-0002, 0005-0006; Tr.515:4-23, 518:5-16, 520:4-523:7, 524:24-526:22, 542:2-8; 875:13-877:9, 878:17-879:9; JTX-471-0003, Fig. 1.

PFF16. As of March 2005, Johnson explained that "[i]n the United States, the sublingual formulation has been recently approved for the treatment of opioid addiction (but not as an analgesic)." (DTX-165-0002.)

PFF17. As of March 2005, Johnson explained that "[i]n the United States, buprenorphine, used as an analgesic, is only approved for parenteral administration, typically by the intramuscular or intravenous route." (DTX-165-0005-06.) These formulations were indicated "for the treatment of moderate to severe pain." (DTX-165-0009.)

Defendants Finding No. 8. The history of buprenorphine is generally set forth in the following timeline:

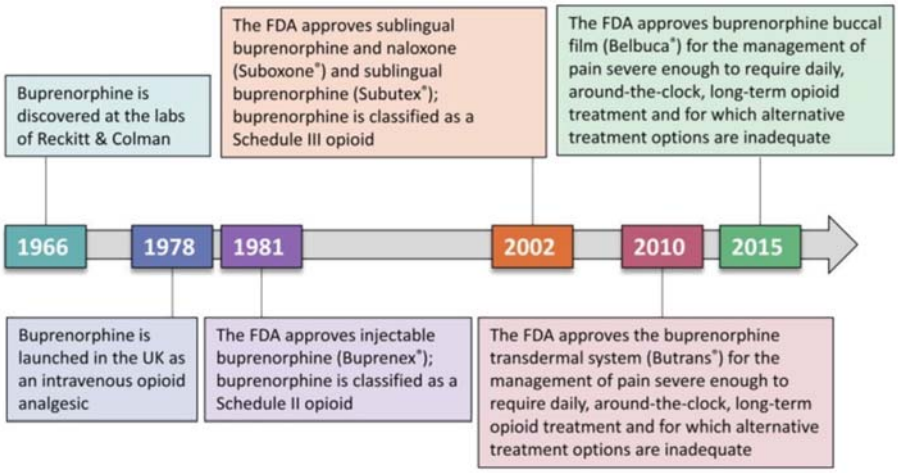


Figure 1. The history of buprenorphine. Buprenorphine was originally developed as an analgesic and was subsequently used for OUD before novel delivery systems allowed for approval in chronic pain management [8,9,12,13]. FDA=Food and Drug Administration; OUD=opioid use disorder.

(DDX1-10; JTX-471-0003; Tr. 480:8-482:19.)

DFF8. Denied. The timeline does not show the entire the history of buprenorphine. It does not include the approval of BELBUCA.

Defendants Finding No. 9. POSAs knew buprenorphine to have "high first pass effect," which means that the liver destroys and renders the buprenorphine less effective if swallowed. (DTX-077-0001; JTX-248-0001; DTX-165-0002, 0005; Tr. 91:2-92:13, 94:20-95:3, 97:12-18.)

DFF9. Admitted.

Defendants Finding No. 10. Because of its known first pass effect, POSAs attempt to formulate buprenorphine as intravenous solutions, nasal sprays, sublingual tablets and buccal films. (DTX-077-0001; JTX-248-0001; DTX-165-0002; Tr. 91:10-19, 92:14-18, 94:20-95:16, 99:11-15.)

DFF10. Plaintiffs do not understand this Finding and thus deny it. By 2006, the known oral transmucosal buprenorphine formulations had poor bioavailability. (DTX-165-0006-0007, Figure 3.)

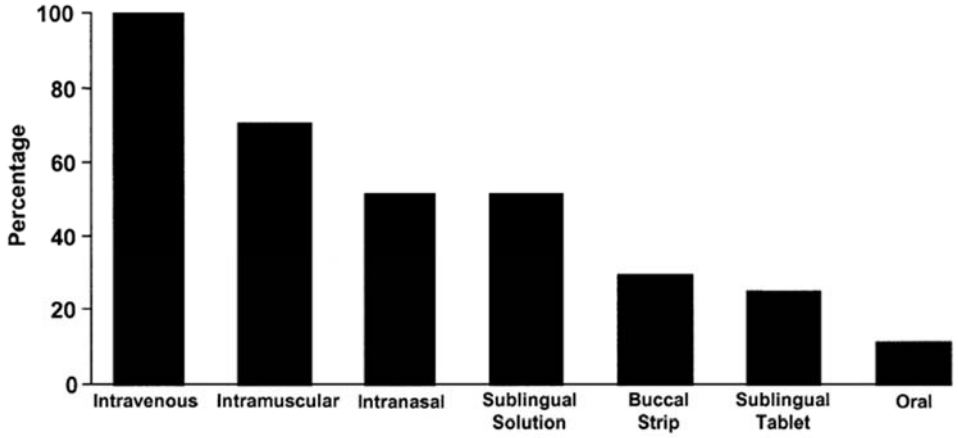


Fig. 3. Approximate bioavailability of buprenorphine by route of administration. Reprinted from Methadone Treatment for Opioid Dependence [Figure 13.2 (c)]. Strain, Eric C., M.D., and Maxine L. Stitzer, Ph.D., eds. The Johns Hopkins University Press. Baltimore, Maryland: The Johns Hopkins University Press, 1999: 300. Reprinted with permission from The Johns Hopkins University Press.

PFF18. Intramuscular injection of buprenorphine had a bioavailability of about 70%. DTX-165-0007, Figure 3; Tr.517:10-15.

PFF19. Sublingual liquid formulations of buprenorphine, like Todd (DTX-174), that used 30% ethanol had a bioavailability of about 30%. DTX-165-0006; Tr.512:8-514:15.

PFF20. Buccal strips available as of 2005 had a bioavailability of about 28 to 35%. DTX-165-0007, Figure 3; Tr.521:6-11; 276:18-21.

PFF21. Suboxone® sublingual tablets have a bioavailability of approximately 25%. DTX-165-0007 at Figure 3; Tr.521:12-522:8; JTX-0365-0004.

PFF22. The oral bioavailability of buprenorphine is approximately 10%. (DTX-165-0002, 0005, 0007 Fig. 3.)

Defendants Finding No. 11. BEMA devices deliver a drug directly to the oral mucosa and thus avoid first pass metabolism. (DTX-173-0001-0002 at abstract, [0002]; JTX-248-0001-0002; Tr. 106:12-107:3, 109:12-21.)

DFF11. Denied. "BEMA devices" within the meaning of the patents-in-suit did not exist in the prior art. *See Resp*. DFF1. Further, JTX-248 (Cassidy), cited by Defendants, teaches non-woven and hydrogel formulations. (Tr.269:9-11.)

Defendants Finding No. 12. Dr. Michniak-Kohn testified about the working mechanism of BEMA devices. (Tr. 131:19-134:9.) Generally, the user applies the BEMA device to the cheek inside the mouth ("buccal surface"). (Tr. 132:3.) Saliva in the mouth (which is mostly water) activates the mucoadhesive polymers, causing the BEMA device to adhere to the mouth. (Tr. 132:3-13.) As the saliva penetrates the BEMA device, the polymers in the mucoadhesive layer begin to swell. (Tr. 132:14-17). The pH buffers dissolve in the saliva and lower its pH, allowing it to dissolve and ionize the buprenorphine. (Tr. 132:14-20; 132:22-133:6, 133:15-21.) The dissolved and ionized buprenorphine then moves through the mucoadhesive layer by concentration gradient and permeates the mucosal surface, where it is absorbed into the bloodstream. (Tr. 133:10-134:2.)

DFF12. Denied. To the extent this finding is meant to describe how the inventions claimed in the '866 or '843 patents function, Plaintiffs disagree with Dr. Michniak-Kohn's description for the reasons set forth in PFF23-28.

PFF23. The invention claimed in the patents-in-suit achieved increased solubility because buprenorphine was "molecular dispersed or dissolved" in the polymers and other excipients of the

mucoadhesive layer creating what is referred to as a "solid solution." Tr.588:9-20, 621:15-622:12, 751:10-752:3.

PFF24. Unlike Dr. Michniak-Kohn, who theorized that the buprenorphine is present in the invention as solid particles, and then must first to "go into the water or the saliva and have to become soluble" to cross the mucosa (Tr.153:12-20, 131:24-132:8), Dr. Williams (and Dr. Vasisht) explained that buprenorphine is *already* dissolved in the polymers and exists as molecules, there are not solid "particles" of buprenorphine that first need to dissolve in saliva. Tr.588:12-20, 611:4-19, 701:16-22, 751:23-752:3,756:24-757:1.

PFF25. The local pH and/or the pH of the saliva, contrary to Dr. Michniak-Kohn, is not the relevant consideration. It is the pH of polymeric diffusion environment where buprenorphine is already solubilized when the mucoadhesive layer is hydrated as it comes into direct contact with the buccal mucosa that is relevant to how the claimed invention functions. Tr.611:20-612:22.

PFF26. Once the mucoadhesive layer attaches to the buccal mucosa, there is a concentration gradient where there are high levels of buprenorphine in the mucoadhesive layer, "[a]nd with that gradient,

that establishes the flux or the diffusion form the mucoadhesive layer directly into the mucosal layer." Tr.586:21-587:19, 593:8-13.

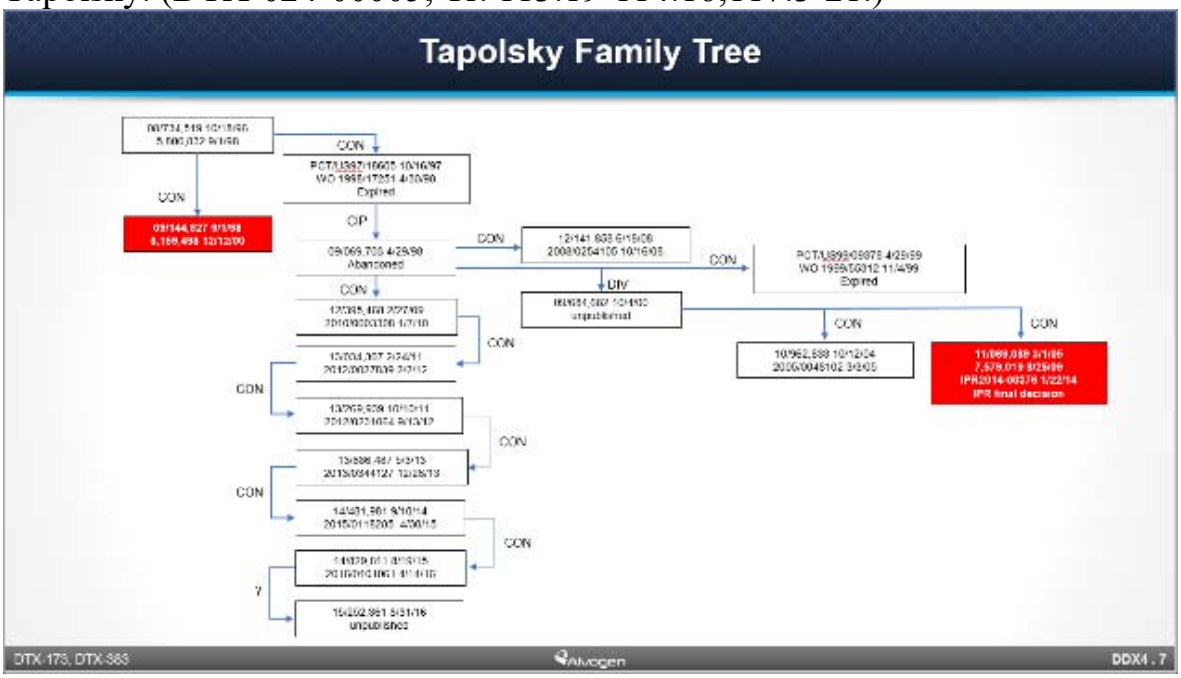
PFF27. Dr. Vasisht was asked whether the buprenorphine becomes "hydrated" when the mucoadhesive film sticks to the surface of the buccal mucosa. (Tr.752:4-10.) Dr. Vasisht responded: "Buprenorphine is in a solution state, dissolved in the mucoadhesive layer. So I -- I don't understand the question in terms of hydration of buprenorphine." (*Id.*)

PFF28. Dr. Michniak-Kohn (who did no testing of her own), has never designed any transmucosal products or formulated any marketed opioid products (Tr.257:21-23, 295:3-296:2), and does not understand the claimed invention better than Dr. Vasisht (who successfully designed and marketed fentanyl and buprenorphine transmucosal products (Tr.755:1-12)) or Dr. Williams (who successfully designed buccal products for the delivery of opioids (Tr.582:3-15).

Defendants Finding No. 13. Saliva and mucous (or mucus) are used interchangeably herein. Each is predominately water. (Tr. 131:19-132:13, 701:13-15.)

DFF13. Denied. The terms saliva and mucous (or mucus) are not interchangeable.

Defendants Finding No. 14. Tapolsky is a family of patents. (Tr. 112:25-113:8.) Tapolsky 2005 is the patent application publication that resulted in U.S. Patent 7,579,019, and is related to U.S. Patents 5,800,832 and 6,159,498, which are incorporated by reference into the '866 and '843 patents. (JTX-001 at 13:1-4; Tr. 113:9-18.) The pharmaceutical development report for BELBUCA states that BEMA technology "followed the invention of the mucoadhesive system described in Patent No. 6,159,498," i.e., Tapolsky. (DTX-024-00005; Tr. 113:19-114:16;117:3-21.)



DFF14. Denied. At trial, the only Tapolsky patent in evidence was Tapolsky-2005, DTX-173. *See* Resp. DFF1. The sentence cited by Defendants states that the BEMA technology "*followed* the invention" of the mucoadhesive system described in Patent No. 6,159,498. This means that the BEMA technology was developed *after* the '498 patent.

Defendants Finding No. 15. Tapolsky discloses the BEMA devices incorporated by reference and claimed by the patents-in-suit for buprenorphine. (JTX-001 at 13:1-4; Tr. 112:24-114:15, 117:3-20.)

DFF15. Denied. *See* Resp DFF1; PFF1-14.

Defendants Finding No. 16. Because Tapolsky discloses more than 200 active agents, including butorphanol, which is a "prototypical agonist-antagonist opioid analgesic agent," a POSA would have reasonably expected Tapolsky's BEMA devices to deliver buprenorphine. (DTX-173 at [0046]-[0053]; DTX-362-0001 at abstract; Tr. 110:18-112:1, 112:16-23, 121:9-17, 129:3-130:19, 261:4-262:3.)

DFF16. Denied. *See* Resp. DFF1-2, PFF1-14.

Defendants Finding No. 17. Tapolsky discloses a BEMA device for any active agent, such as opioids like butorphanol that would benefit from transmucosal delivery. (DTX-173 at [0002], [0013], [0046]-[0053], [0131]; Tr. 106:10-107:3, 111:3-112:4, 112:16-23.)

DFF17. Denied. *See* Resp. DFF1-2, PFF1-14.

Defendants Finding No. 18. The '866 and '843 patents disclose butorphanol as an exemplary opioid amongst 57 other opioids, including buprenorphine. (JTX-001-0010 at 9:58; JTX-002-0012 at 10:9))

DFF18. Denied. The '866 patent identifies butorphanol as an opioid and states that it is "suitable for use." JTX-0001, col. 9:55, 57; *see* PFF2-6.

Defendants Finding No. 19. During prosecution, in a petition to the Commissioner of Patents to accelerate examination of the '866 patent, BDSI stated, "Tapolsky is Applicant's own patent" and, falsely, "does not teach administration of an opioid." (JTX-004-0033.)

DFF19. Denied. During prosecution of the '866 patent, Plaintiffs' attorneys identified "Taposkly et al. US Patent No. 6,159,498" as a prior art reference closely related to the pending claims. (JTX-004-0027.) In discussing that specific reference, Plaintiffs stated that "Tapolsky et al. does not teach administration of an opioid, including buprenorphine, or an opioid antagonist." (JTX-004-0033.) This statement was completely accurate as the '498 patent does

not mention opioids or butorphanol. Tapolsky-2005 (DTX-173), relied on here by Defendants, is a later application containing additional disclosure.

> Defendants Finding No. 20. Tapolsky's BEMA device is for administration to a mucosal (e.g., buccal) surface. (DTX-173 at [0002], [0024], [0027], Example 20, [0100], [0128]; Tr. 129:23-130:19, 109:22-110:17, 247:13-16, 247:25-248:16.) Tapolsky discloses a method for the direct transmucosal administration of drug, which provides effective drug delivery. (D.I. 114 at 4; DTX-173 at [0024]; JTX-001-0009 at 7:9-11; Tr. 106:12-107:3.)

DFF20. Denied. *See* Resp. DFF1, PFF1-14. A POSA would not believe that Tapolsky-2005's experiments in dogs with testosterone and albuterol sulfate could predict how other chemical compounds would behave in humans in Tapolsky's devices. *See* PFF12.

> Defendants Finding No. 21. Tapolsky's BEMA device is a layered film disk including a water-erodable adhesive layer including drug and a water-erodable backing layer. (DTX-173 at [0013], [0030]; Tr. 106:17-107:3.)

DFF21. Plaintiffs deny that Tapolsky describes a "BEMA device" as discussed in Resp. DFF1.

> Defendants Finding No. 22. Tapolsky's BEMA device contains an adhesive layer including a film-forming water erodible polymer, such as hydroxyethyl cellulose or hydroxypropyl cellulose, and a bioadhesive polymer, such as sodium carboxymethylcellulose. (DTX-173 at [0031]-[0032]; Tr. 107:4-6, 107:15-109:4; *see* D.I. 249 at 2.)

DFF22. Denied. Tapolsky-2005 states that the film "may" comprise such polymers. Plaintiffs deny that Tapolsky-2005 describes a "BEMA device" within the meaning of the patents-in-suit. See Resp. DFF1; DTX-173, ¶¶ 0031-32.

> Defendants Finding No. 23. Tapolsky's polymers for the adhesive layer are the same polymers described in the patents-in-suit and utilized in BELBUCA. (JTX-233-023; DTX-173 at [0031]-[0032]; JTX-001-012 at 13:62-63, 14:12; JTX-002-014 at 14:19-20, 14:36-37; Tr. 108:11-18.)

DFF23. Denied. Tapolsky-2005 (DTX-173) describes the polymers cited in this finding, but *only* amongst a long list of other polymers. *See* Resp. DFF22. Defendants have not shown in this finding, or in any other, that Tapolsky-2005 describes the specific combination of polymers in the amounts used in the adhesive layer that are described in the patents in suit or that are used in BELBUCA. *See e.g*. JTX-001, Example 1; DTX-019-0031.

> Defendants Finding No. 24. Tapolsky's BEMA device also contains a non-adhesive backing layer disposed adjacent to the adhesive layer to provide unidirectional delivery of the drug towards the mucosal surface and to minimize swallowing. (DTX-173 at [0020], [0021], [0030], [0058]-[0062], FIG. 1, FIG. 2; Tr. 109:12-21).

DFF24. Denied. *See* Resp. DFF1. Tapolsky-2005 describes using a third layer to obtain unidirectional release. DTX-0173, ¶ 58; Tr.109:12-21; Resp. DFF1; PFF14.

> Defendants Finding No. 25. Tapolsky discloses a unidirectional diffusion gradient that saliva penetrates in order to move the drug across the polymeric diffusion environment upon application of the device to a mucosal surface. (DTX-173 at [0020], [0021], [0030], [0058]-[0062], FIG. 1, FIG. 2; Tr. 106:20-107:3, 109:12-21, Tr. 109:12-110:17, 129:23-130:19, 247:13-16, 247:25-248:16.)

DFF25. Denied. *See* Resp. DFF24. Defendants' citations do not support this finding.

Defendants Finding No. 26. Tapolsky discloses suitable polymers for the backing layer, including a water-erodible, film-forming polymer such as hydroxyethyl cellulose or hydroxypropyl cellulose. (DTX-173 at [0035]; Tr. 109:5-11; *see* D.I. 249 at 2.)

DFF26. Denied. DTX-173 states that the "non adhesive backing layer *may* comprise a water-erodable, film-forming pharmaceutically acceptable polymer" and then describes many different polymers. Among the polymers described are hydroxyethyl cellulose and hydroxypropyl cellulose. DTX-173, ¶ 35.

Defendants Finding No. 27. Tapolsky's polymers for the backing layer are the same polymers described in the patents-in-suit and utilized in BELBUCA. (JTX-233-0023; JTX-001-0013 at 15:36; JTX-002-0015 at 15:62-63; Tr. 107:15-108:10, 109:7-11.)

DFF27. Denied. Tapolsky-2005 (DTX-173) describes the cited polymers, but *only* amongst a long list of other polymers. Defendants have not shown in this finding, or in any other, that Tapolsky-2005 describes the specific combination of polymers in the amounts used in the backing layer that are described in the patents in suit or that are used in BELBUCA. *See* e.g. JTX-001, Example 1; DTX-019-0031.

Defendants Finding No. 28. Tapolsky's BEMA devices "yield fast onset of activity," i.e., rapid and efficient delivery, as well as "excellent bioavailability, and sustained delivery," i.e., enhanced uptake. (DTX-173-0015 at [0131]; *see also* DTX-173-0001 at abstract; Tr. 106:17-107:3.)

DFF28. Denied. *See* Resp. DFF1. The quoted statements refer to experiments in dogs with testosterone and albuterol sulfate and are *not* generally applicable to all chemical compounds, including buprenorphine. PFF7.

> Defendants Finding No. 29. Tapolsky's BEMA devices provide drug delivery that achieves effective plasma concentration beyond four hours. (DTX-173 at Table 5; Tr. 346:2-14.)

DFF29. Denied. *See* Resp. DFF1. Tapolsky-2005 does not teach a POSA that its devices would provide effective plasma concentrations of buprenorphine, for at least 4 hours. Tapolsky-2005 does not discuss what an effective dose of albuterol sulfate is and does not even mention buprenorphine. Tr.262:13-15, 422:24-423:2; Tr.810:15-20; PFF10.

> Defendants Finding No. 30. Like Tapolsky, Moro discloses BEMA technology incorporated by reference by the patents-in-suit. (JTX-001 at 13:1-4; DTX-178 at [0001], [0010], [0035], [0046]; Tr. 117:22-118:11, 121:2-121:6, 121:18-25.)

DFF30. Denied. Moro does not describe "BEMA" technology. Moreover, the patents-in-suit do not "incorporate by reference" BEMA technology. *See* Resp. DFF1, PFF29-36.

> **PFF29.** While buprenorphine is mentioned in Moro, it is mentioned as part of a laundry list of chemical compounds and categories of chemical compounds. DTX-178, ¶¶17-24.
>
> **PFF30.** Moro does not disclose the "rapid and efficient delivery" of an active ingredient, as that term is used in the '866 patent. DTX-178.

PFF31. Moro describes devices that provide "a sustained level of drug [delivery] at a more controlled rate over a longer treatment time." (DTX-178, ¶46.) The devices of Moro have a residence time of between 40 and 240 minutes. (DTX-178, ¶92.)

PFF32. There is no example in Moro of using any pharmaceuticals or any active agent in the devices of Moro, much less buprenorphine, and thus there is no experimental data concerning how any such device would behave and certainly no evidence of enhance uptake. *See* Tr.262:22-24, 263:5-7.

PFF33. There is no evidence in the record that Moro ever became a commercial product. Tr.264:7-9.

PFF34. Moro teaches that a backing layer, not an adhesive layer, is bioerodible. The adhesive layer is referred to as water soluble. DTX-0178, ¶10; Tr.263:23-25.

PFF35. The examiner considered Moro during prosecution of the '843 and '866 patents and held that Moro did not render the claims of either patent obvious. JTX-0001-0001, Item (56); JTX-0005-2784.

PFF36. Moro does not disclose a polymeric diffusion environment buffered to a particular pH. Tr.654:23-25; D.I 249, at 4.

Defendants Finding No. 31. Moro discloses an extensive list of active agents. (DTX-178 at [0047]-[0065]; Tr. 120:8-16). Moro discloses a BEMA

device for any active agent that would benefit from transmucosal administration. (DTX-178 at [0035], [0047]-[0065]; Tr. 118:8-11.)

DFF31. Denied. Moro does not describe a BEMA device. *See* DFF1. Moreover, the cited testimony does not support the statement that Moro discloses "device for any active agent that would benefit from transmucosal administration." *See* PFF12, 28, 29-36.

Defendants Finding No. 32. Moro discloses BEMA delivery of "analgesic narcotics," including buprenorphine specifically. (DTX-178-0005-0008 at [0035], [0046], [0064]; Tr. 117:22-118:11, 118:12-22, 120:13-16.)

DFF32. Denied. Moro does not describe BEMA delivery. *See* DFF1, 11, 30. Moro describes buprenorphine as being an "analgesic narcotic." DTX-178, ¶64. Moro does not describe any experiments that deliver any active agent, much less buprenorphine. *See* PFF32.

Defendants Finding No. 33. The Moro device contains an adhesive layer including a film-forming polymer, such as hydroxyethyl cellulose or hydroxypropyl cellulose, and a bioadhesive polymer, such as sodium carboxymethylcellulose. (DTX-178-0006 at [0041]; Tr. 118:23-119:10; *see* D.I. 249 at 4.)

DFF33. Admitted.

Defendants Finding No. 34. The Moro device also contains a non-adhesive backing layer including a film-forming polymer such as hydroxyethyl cellulose or hydroxypropyl cellulose (*see* D.I. 249 at 4), which maximizes unidirectional delivery of drug toward the mucosal surface while minimizing swallowing of the drug. (DTX-178-0006 at [0043]; Tr. 119:11-120:7.)

DFF34. Denied. Moro does not single out hydroxyethyl cellulose or hydroxypropyl cellulose as important polymers to use in the backing layer for unidirectional delivery.

> Defendants Finding No. 35. Moro's polymers for the mucoadhesive and backing layers are the same polymers described by the patents-in-suit and utilized in BELBUCA. (JTX-233-0023; DTX-178-0006 at [0041], [0043]; JTX-001-0012-0013 at 13:62-63, 14:12, 15:36; JTX-002-0014-0015 at 14:19-20, 14:36-37, 15:62-63; Tr. 108:11-18, 118:23-119:17.)

DFF35. Denied. Moro describes the cited polymers amongst a long list of other polymers. Defendants have not shown in any proposed finding that Moro describes the specific combination of polymers in the amounts used in the adhesive layer or backing layer that are described in the patents in suit or that are used in BELBUCA. (*See e.g.*, JTX001, Example 1; DTX-019-0031.)

> Defendants Finding No. 36. Buprenorphine hydrochloride[2] is the salt form of buprenorphine that formulators use in pharmaceutical formulations. (*See* JTX-003-0012 at 9:61-62; JTX-248-0002.) n.2: The terms "buprenorphine" and "buprenorphine hydrochloride" are used interchangeably herein.

DFF36. Denied. This finding is vague as it does not define what formulators or formulations are referenced and at what time period. Defendants' cited evidence does not support this finding.

> Defendants Finding No. 37. Buprenorphine is a BCS-II ("Biopharmaceutics Classification System - Class II") drug, which means that the drug has low solubility in saliva but high permeability (lipophilicity). (Tr. 699:18-701:5.)

DFF37. Denied. *See* PFF46-50. Defendants have not put forward any evidence in the record demonstrating that the BCS classification system was known as of 2006. Further, the cited testimony does not substantiate the assertion that buprenorphine "has low solubility in saliva."

> Defendants Finding No. 38. If the formulation buffers the saliva to a pH capable of ionizing and dissolving the buprenorphine, then the buprenorphine will readily permeate the mucosal membranes and absorb into the bloodstream. (Tr. 131:19-134:9, 699:18-701:5.)

DFF38. Denied. It is unclear what formulations or what devices at what time periods this finding refers to. Further, in the claimed inventions, the buprenorphine is already solubilized in the polymeric diffusion environment and is not in the form of solid particles that need to be dissolved by salvia. *See* PFF23-28. Further, the evidence does not show that buprenorphine "readily" permeated the mucosa if it was soluble. The bioavailability for sublingual liquid formulations with aqueous ethanol were only about 30% and for sublingual tablets was only about 25%. *See* PFF19, 21.

> Defendants Finding No. 39. Johnson summarizes what POSAs knew about buprenorphine prior to the patents-in-suit. Specifically, that buprenorphine: (1) is a highly potent and effective analgesic for the treatment of pain with a long duration of action; (2) has a wider safety profile compared to other opioids, especially with regard to respiratory depression; (3) has low abuse potential and fewer symptoms of withdrawal; (4) experiences high first pass effect (and should be administered transmucosally, for example, to avoid liver metabolism); and (5) is extremely lipophilic (meaning that it will permeate mucosal membranes when dissolved and ionized). (DTX-165-0001-0003, 0005, 0007-0009, 0020-0021; Tr. 96:4-98:22, 484:25-486:25.)

DFF39. Denied. Buprenorphine was not shown to be effective for chronic pain in the United States as of 2006. *See* PFF15-16, 65-66. Further, for points (2) and (3), Johnson is merely theorizing by using the word "may." (DTX 165-0002.) Plaintiffs agree that buprenorphine was known to have a high first pass effect and lipophilic. (DTX-0165-0005.)

> Defendants Finding No. 40. At trial, BDSI agreed that Johnson teaches that buprenorphine has limited abuse potential because of a ceiling effect at higher doses, and has a wider safety potential compared to full mu agonists. (DDX4-5; Tr. 143:23-24.)

DFF40. Admitted.

> Defendants Finding No. 41. Bullingham I discloses the same properties of buprenorphine described in Johnson. (DTX-077-0001, 0005; Tr. 91:2-19, 93:25-94:9.) Bullingham I teaches that buprenorphine was well suited for oral transmucosal administration because of its high lipophilicity, high potency, high first pass effect, long duration of action, and low abuse potential. (DTX-077-0001; Tr. 91:2-19, 92:19-25, 99:7-10; *see* D.I. 249 at 3.) Bullingham I teaches that sublingual delivery of buprenorphine is effective because of these "specific features of buprenorphine." (DTX-077-0005; Tr. 93:25-94:9; *see also* JTX-248-002.)

DFF41. Denied. Bullingham-I does not show to a POSA that sublingual tablets were actually effective because the data was compromised due to the design of the study that intermixed intravenous and sublingually administered buprenorphine. Tr.812:12-814:17, 408:10-19; DTX-077-0002; PFF37-45.

> Defendants Finding No. 42. Bullingham I reports that the sublingual (i.e., transmucosal) administration of buprenorphine provides a first quantifiable concentration (i.e., Tfirst) of buprenorphine between 40 and 60 minutes once the background intravenous dose is excluded. (DTX-077-0003 (Table 2); Tr. at 334:10-335:17.)

DFF42. Denied. *See* PFF37-45.

PFF37. Bullingham I purports to investigate the pharmacokinetics of buprenorphine following sublingual tablet administration but only after patients already received intravenous buprenorphine the same day. As such, the pharmacokinetic data from the study as relating to the sublingual tablet is compromised and unreliable. Tr.403:14-20, 408:10-19, 812:12-816:25; DTX-077-0002-0003.

PFF38. Dr. Taft testified: "If you look at the plasma levels of buprenorphine from the intravenous dose at the time the sublingual tablets were introduced, that's the primary contributor to the plasma levels that were measured in the patient. That between 0 and 45 minutes after the tablets were introduced, the intravenous [] dose is what's driving the effect." (Tr.818:2-9.)

PFF39. The "stripping" technique used by Bullingham I introduced significant error and rendered the data unreliable. (Tr.813:11-814:4.) The "stripped" estimated plasma buprenorphine from the intravenous dose in Bullingham-I was calculated from an earlier study with a different group of patients. (Tr.812:12-814:4, 408:10-19.) For this reason, within the first hour where the intravenous contribution is most prevalent, a POSA would understand that pharmacokinetic data

for sublingual tablets are not reliable. (Tr.814:5-17.) Any analgesic effect occurring between 15 and 45 minutes would be contributed to residual plasma buprenorphine from the initial intravenous dose, not the sublingual buprenorphine tablets. Tr.814:5-17, 817:18-820:3, 405:8-22, 406:22-408:9; DTX-0077-0003-4.

PFF40. In Bullingham I, a POSA would not be able to tease out the duration of analgesia due solely to buprenorphine absorbed from the sublingual tablets. Tr.811:11-822:14.

PFF41. Table 2 of Bullingham I shows the problem with the data. It reports a value of 0.10 ng/ml at 40 minutes, plus or minus 0.12, which is the standard error of the mean. (DTX-077-0003; Tr.815:23-816:1.) This suggests that "within one standard error the value is 0. It's not detectable." *Id*. And applying the standard deviation results in a negative value. (Tr.816:2-15.) A POSA would understand that this is not a quantifiable concentration. (Tr.816:16-25.)

PFF42. Bullingham-II, another study by the same authors as Bullingham-I, also reports estimated plasma buprenorphine concentrations following administration of sublingual buprenorphine tablets, which are calculated using the same "stripping" method discussed above. Tr.823:11-825:1; DTX-177-0002-3.

PFF42.1 As with Bullingham-I, the reported plasma buprenorphine concentrations for the sublingual tablets in Bullingham II are influenced by the preexisting intravenous dose and are unreliable. Tr.812:4-814:17, 823:11-825:1; 408:10-19, 419:14-18; DTX 177-0002-3, 0005.

PFF42.2 Table 6 of Bullingham II shows that the first measurable plasma concentration due to the sublingual tablets occurred at 60 minutes, not 45 minutes. DTX-177-0007; (Tr.823:11-824:6, 825:2-11, 410:4-8). Before this time, the plasma concentration due to the sublingual tablets is zero. *Id*.

PFF43. Bullingham I also does not show an effective plasma concentration for at least four hours because of the compromised data due to the effect of intravenous administered buprenorphine. *See* PFF37. Bullingham I does not even mention the plasma concentration of buprenorphine after 3 hours—180 minutes was the last measurement. (Tr.820:12-821:4.) As such, Bullingham I, could not possibly report an effective plasma concentration from the sublingual tablets for at least 4 hours. *Id*.

PFF44. A POSA would not view Bullingham I as showing that patients experienced analgesia for more than four hours, or "534

minutes," due to the design of the study, which intermixed intravenous buprenorphine data and also allowed a "pump" that delivered yet another drug to the patient, diamorphine. Tr.821:5-822:14, 409:18-22; DTX-077-0002.

PFF45. Bullingham II provides a plasma concentration that the authors consider minimally effective: "plasma drug concentrations as low as 0.4 to 0.6 ng/ml are associated with appreciable analgesic effect." DTX-177-0005; Tr.825:15-23. For the .4 mg sublingual tablet (the same dose in Bullingham-I), Table 6 shows a plasma concentration reaching .4 ng/ml at 180 minutes, and then falls below this concentration at 240 minutes. Tr.826:20-827:15. Thus, Bullingham-II reports an effective plasma concentration for at most 90 minutes not at least four hours. Tr.416:18-23.

Defendants Finding No. 43. At trial, BDSI agreed that Bullingham I teaches that buprenorphine is highly potent, has a long duration of action with low abuse potential, and is highly lipophilic. (DDX4-5; Tr. 142:24-143:11; *see also* D.I. 249 at 3.)

DFF43. Denied. BDSI explained that buprenorphine is highly lipophilic when it is not in an ionized state. (Tr.142:20-23.)

Defendants Finding No. 44. Bullingham I discloses that the onset of pain relief from the sublingual dose of buprenorphine "occurred between 15 and 45 minutes." (DTX-077-0003; Tr. 338:25-339:20).

DFF44. Denied. *See* PFF37-45.

Defendants Finding No. 45. Bullingham I also discloses that the sublingual administration of buprenorphine maintains an average duration of analgesia for 534 minutes. (DTX-077-0003.) Bullingham I teaches maintaining effective buprenorphine concentrations for more than four hours. (DTX-077-0003; Tr. 344:16-345:7.)

DFF45. Denied. *See* PFF37-45.

Defendants Finding No. 46. Saliva is not ideal for dissolving buprenorphine due to its near-neutral pH. (JTX-249-0004; Tr. 133:15-21, 147:7-23.)

DFF46. Denied. The cited evidence does not support this finding. In addition, it is not relevant to the operation of the claimed invention. *See* PFF23-28; Tr.611:1-612:22.

Defendants Finding No. 47. pH is the measure of how acidic or basic a liquid is relative to neutral water. (Tr. 146:11-147:4.) pH is logarithmic, such that each unit is an order of magnitude greater or lesser than its adjacent units. (Tr. 146:20-147:4.) For example, a pH of 4 is 10X more acidic than a pH of 5 and 100X more acidic than a pH of 6. (See Tr. 146:13-147:6.)

DFF47. Denied. The cited testimony does not substantiate the assertion that "pH is the measure of how acidic or basic a liquid is relative to neutral water." Plaintiffs admit that the pH scale is logarithmic.

Defendants Finding No. 48. POSAs understood buprenorphine to be poorly soluble in water. (Tr. JTX-248-0004, 0007-0008, Tr. 131:19-133:21, 153:9-24.)

DFF48. Denied. Solubility of buprenorphine depends on many factors, including the solvent system and the pH. This finding cites Cassidy (JTX-248-0004), but Cassidy used buffered solutions, not water.

Defendants Finding No. 49. POSAs also understood that buprenorphine solubility is highly pH-dependent, having the highest solubility at low (i.e., strongly acidic) pH values. (JTX-248-0004; Tr. 147:7-23; 166:12-23.)

DFF49. Denied. The solubility of buprenorphine depends on the particular system. For example, the polymeric diffusion environment of the claimed invention has different solubility properties than Cassidy. (Tr.756:20-757:1, 762:13-763:9; (*Compare* DTX-024-0024 (Fig. 3) *with* JTX 248 0012 (Fig 1); Tr.622:13-624:3, 624:17-23; DTX 071-0021 (Fig. 7); DTX 370-0020 (Fig. 7)); (JTX 0005-2771).

Defendants Finding No. 50. "Solubility" is the maximum concentration of drug than can dissolve in a solvent (e.g., water). (Tr. 139:1-2.)

DFF50. Admitted.

Defendants Finding No. 51. "Dissolution" is the rate the drug dissolves in the solvent. (Tr. 139:3-4.)

DFF51. Admitted.

Defendants Finding No. 52. At acidic pH values below 6, buprenorphine is ~100% ionized. (JTX-248-0004; Tr. 133:2-133:6, 133:15-21; 166:12-23, 175:3-6, 671:16-672:7.)

DFF52. Denied. Plaintiffs deny that this information had been calculated or was published as of 2006. (*See* Resp. DFF-65.) Further, that Dr. Davies testified that the nonionized form of buprenorphine only appears in a significant amount between about pH 6 and 12, does not mean that there is no nonionized form of buprenorphine below pH 6. (Tr.730:10-18.)

> Defendants Finding No. 53. "Ionization" is the process by which the neutral drug salt converts to electrically charged "ions" in solution. (Tr. 139:5-6.) Like solubility, ionization of buprenorphine is highly pH-dependent. (Tr. 146:8-12.)

DFF53. Denied. The percentage of buprenorphine molecules that exist in each protonation state changes depending on the pH. (DTX-377-0004; Tr.728:9-729:5.)

> Defendants Finding No. 54. The entire prior art of record demonstrates that formulators provided buprenorphine in acidic pH environments where it is ~100% ionized. (JTX-249-0006; DTX-377-002-0004; Tr. 168:24-170:22, 162:14-164:9, 170:6-9; DTX-172-0004; Tr. 167:18-168:23; DTX-203 at [0010], [0071], [0083]; Tr. 171:3-172:22; DTX-174-0003-0004 at 2:11-3:4; Examples 1-18; Tr. 174:13-175:6, 671:16-673:25.)

DFF54. Denied. There is no evidence in the record that anyone had actually calculated or published the ionization states of buprenorphine as of 2006. *See* Resp. DFF65; PFF46-50.

> **PFF46.** The prior art as a whole taught that for a weakly basic drug, bioavailability and absorption would increase as the pH increases, and the drug becomes more unionized. JTX 249-0006, 0007; JTX-250, col.4:49-58; JTX-246-0001; JTX-462, ¶53; JTX-243, col.4:58-62; (Tr.251:2-9, 629:22-630:6, 644:19-647:25, 706:20-707:3, 797:1-800:7). This is consistent with the partition theory. (Tr.730:19-731:21, 795:1-16, 796:13-25.)

PFF47. A POSA would have expected that at higher pHs, buprenorphine primarily nonionized, which would lead to a higher partition coefficient and lipophilicity. (Tr.795:17-796:12.)

PFF48. Weinberg teaches that for weakly basic drugs, including buprenorphine, absorption and bioavailability increases as the pH increases and the drug becomes less ionized. JTX 249-0006, 0007; (Tr.629:22-630:6, 645:20-646:6, 706:20-707:3, 797:4-21). This was confirmed by Dr. Michniak-Kohn's book. (DTX-355-0011.)

PFF49. Todd confirms this trend, stating that uptake of buprenorphine increased as the pH increased. DTX-174-0003.

PFF50. The entire prior art of record teaches away from using lower pH values to obtain enhanced bioavailability. *See* PFF46-48. For example, liquid formulations like Todd (containing ethanol) with a pH between 4.5-5.5 had a bioavailability of approximately 30%. PFF19. But the sublingual solution in Weinberg with a pH of 6.5 had a bioavailability of approximately 55%. JTX-249-0006. Further, a POSA would have been reluctant to put buprenorphine at a low pH, such as from pH 4 to 6, because of the risk of buprenorphine undergoing decomposition reactions. (Tr.745:20-747:19.)

Defendants Finding No. 55. None of the prior art relied on by Dr. Williams teaches that buprenorphine is subject to a "general rule" that unionized drugs permeate the mucosa better. (Tr. 664:11-670:20.)

DFF55. Denied. *See* Resp. DFF54, PFF46-50.

Defendants Finding No. 56. The trial record does not include any reference where a formulator attempted to provide buprenorphine in a neutral or basic environment, or where the buprenorphine was less than ~100% ionized. (Tr. 176:1-176:9, 201:14-202:17.)

DFF56. Denied. Weinberg shows that weakly basic drugs such as buprenorphine are absorbed better as the pH increases and the drug becomes less ionized. JTX 249-0006, 0007; (Tr.629:22-630:6; 645:20-646:6, 706:20-707:3, 797:1-21). Dr. Davies testified that the pH of 6.5 used in Weinberg is between 6 and 12 and is in the range Dr. Davies identified as having non-ionized buprenorphine present in significant amounts. (Tr.730:13-15, 734:9-13, 741:17-21.) Further, the inventors formulated buprenorphine films at pH 7.25, which was completely soluble. (Tr.648:15-650:4, 754:21-756:2, 759:19-760:11); JTX-365-0004.

Defendants Finding No. 57. Cassidy teaches that the solubility of buprenorphine is highly pH dependent, with the highest solubility seen at low (acidic) pH. (JTX-248-0004; Tr. 147:7-23.)

DFF57. Denied. The teachings of Cassidy are limited to the particular buffered liquid systems investigated therein. (JTX-248-0004.) Every system is different, and the polymeric diffusion environment of the claimed invention has different solubility properties than Cassidy. DFF49; JTX-248-0004.

PFF51. The solubility of buprenorphine in the polymers of the mucoadhesive layer is different than that reported for simple buffer solutions in Cassidy, and has dramatically increased solubility of buprenorphine at the pH ranges thought to be most useful to obtain enhanced bioavailability, which are on the right side of the below chart. (Tr.624:17-23, 706:5-19.)

(*Compare* DTX-24 at p. 12 (Fig. 3) *with* JTX 248-0012 (Fig 1); Tr.622:13-624:23; DTX 071-0021 (Fig. 7); DTX 370-0020 (Fig. 7).)

PFF52. As stated by Dr. Vasisht, the "polymeric diffusion environment of [the] present claims is a three-dimensional dynamic system where the buprenorphine is solubilized in the system, wherein the solubility is not the solubility in an aqueous environment . . . Accordingly, information about solubility in an aqueous system does

not translate to a polymeric diffusion environment." (JTX 0005-2771.)

Defendants Finding No. 58. Cassidy teaches that buprenorphine solubility at "neutral pH," i.e., pH 7.3, is "considerably lower." (JTX-248-0004; Tr. 147:7-23.

DFF58. Denied. *See* DFF 57; PFF 51-52.

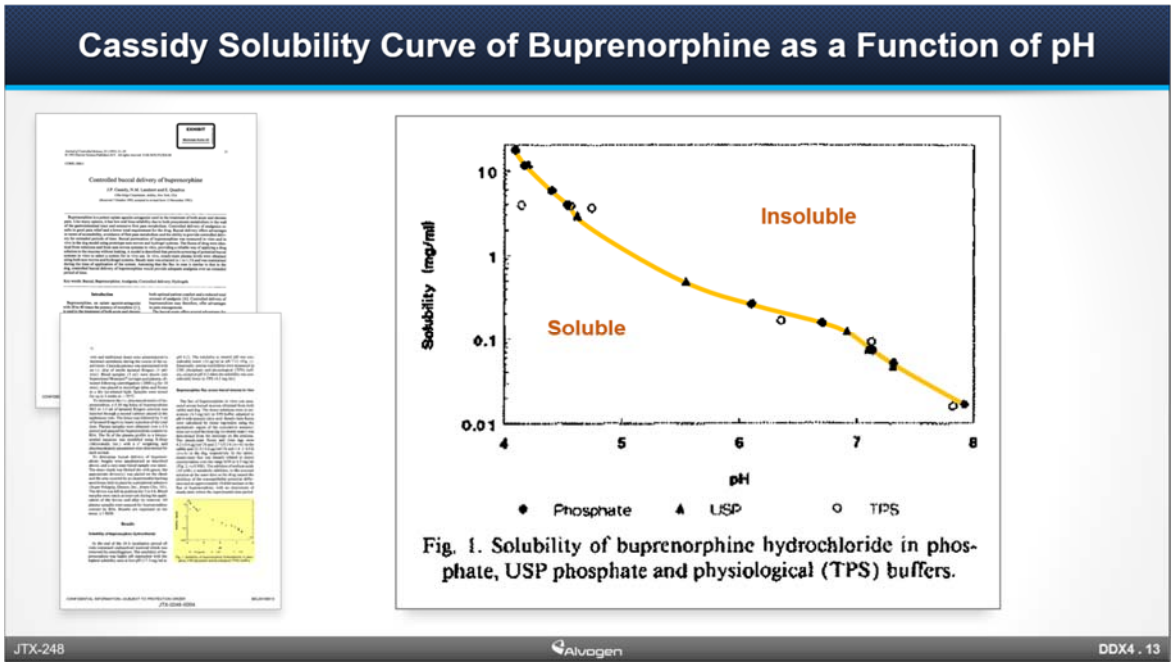
Defendants Finding No. 59. Figure 1 of Cassidy illustrates buprenorphine solubility, i.e., the amount of buprenorphine (mg/mL) that can be dissolved in each of three different buffers, i.e., phosphate, USP phosphate, and physiological (TPS), versus pH (from 4 to 8) on a logarithmic scale. (JTX-248-0004 at Figure 1; Tr. 138:14-139:2, 147:24-148:14.)

DFF59. Denied. Cassidy shows the solubility of buprenorphine in three different liquid buffer systems (phosphate, USP phosphate and physiological (TPS buffers)). Plaintiffs deny that such solubility applies to other systems. *See* Resp. DFF-57; PFF51-52.

Defendants Finding No. 60. Cassidy reports that similar buprenorphine solubilities were measured in each buffer system, except at pH 4.2, where buprenorphine solubility in TPS buffer was "considerably lower" than in the other two buffers because of the reduced buffering capacity of TPS at this low pH. (JTX-248-0004; Tr. 148:15- 150:9). The point at pH 4.2 in TPS buffer is an outlier. (JTX-248-0004; Tr. 148:15-150:9.)

DFF60. Denied. The data point for TPS buffer at 4.2 is as valid as any other data points and is not characterized as an "outlier." JTX-248-0004.

Defendants Finding No. 61. Setting aside the point at pH 4.2 for TPS buffer, which Cassidy characterizes as an outlier, Dr. Michniak-Kohn annotated Figure 1 as follows:



(DDX 4-13; JTX-248-0004 at Figure 1; Tr. 148:15-150:9, 150:19-151:5.)

DFF61. Denied. Cassidy states that data point for TPS buffer at 4.2 is different. It does not characterize it as an outlier. JTX-248-0004; DFF57, PFF51-52.

Defendants Finding No. 62. Points that fall below the line represent soluble buprenorphine, while points that fall above the line represent insoluble buprenorphine. (JTX-248-0004 at Figure 1; Tr. 150:19-151:5.)

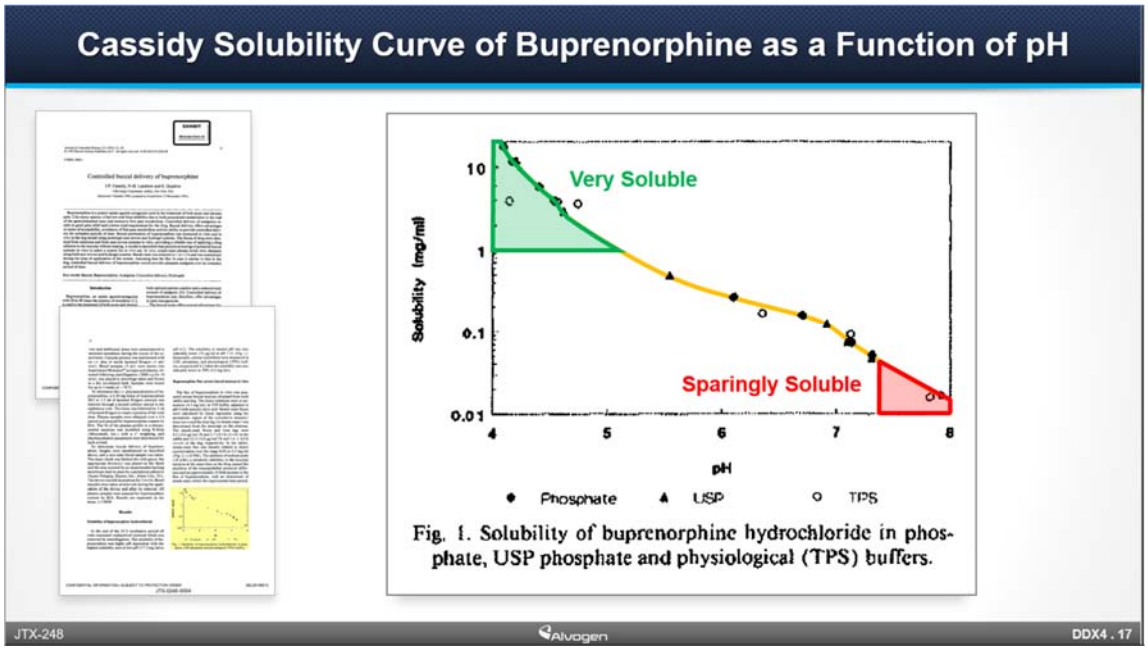
DFF62. Denied. The data in Cassidy only applies to the liquid buffer systems examined. *See* Resp. DFF57; PFF51-52.

Defendants Finding No. 63. Figure 1 of Cassidy illustrates that the highest solubility of buprenorphine is obtained below a pH of about 5. (JTX-248-0004 at Figure 1; Tr. 150:12-18.)

DFF63. Denied. *See* Resp. DFF57; PFF51-52.

Defendants Finding No. 64. Figure 1 of Cassidy (as annotated by Dr. Michniak-Kohn) illustrates that buprenorphine is "very soluble" at pH values below 5, and is "sparingly soluble" to insoluble at pH values above

7.5.



(DDX 4-17; Tr. 151:25-153:2.)

DFF64. Denied. *See* Resp. DFF-57; PFF-51-52.

Defendants Finding No. 65. Based on the calculations performed by Dr. Stephen Davies (BDSI's chemistry expert), a POSA would have understood that buprenorphine is 100% ionized at pH values below 5 where it is "very soluble." (DTX-377-0002, 004; Tr. 162:14-164:19; 165:21-166:11.) (DDX 4-20.)

DFF65. Denied. There is no evidence that the ionization states for buprenorphine were actually calculated or published in the prior art as of 2006, using the Henderson-Hasselbalch equation. (Tr.163:21-164:2.) Plaintiffs further deny that the solubility of Cassidy applies to all systems. *See* Resp. DFF-57; PFF-51-52.

PFF53. If a POSA were to calculate the ionization states in the prior art, a POSA would have understood that the unionized form of

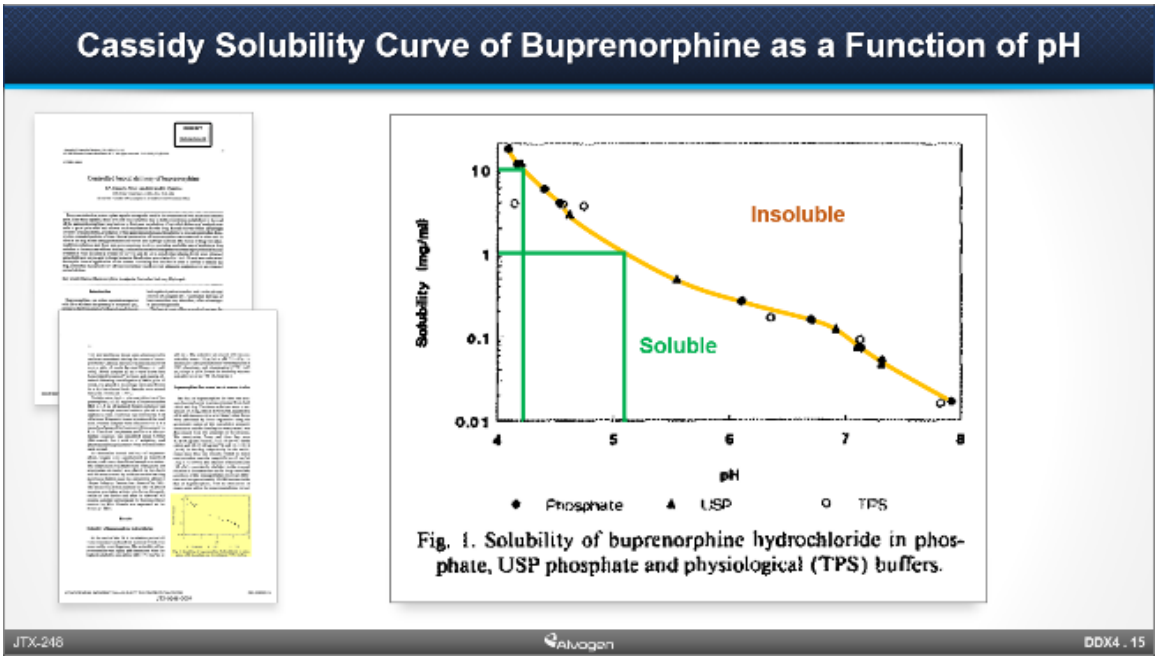
buprenorphine is between 6 and 12 and that the unionized form is desired to increase absorption and bioavailability. (Tr.730:4-731:10; 795:1-800:7.)

PFF54. A POSA, in possession of the ionization states of buprenorphine in 2006, would have been motivated to use pH's higher than 6 to obtain enhanced uptake and increased bioavailability. (Tr.730:13-15, 734:2-13, 741:12-20, 799:21-800:7.)

Defendants Finding No. 66. A POSA would have been able to generate Dr. Davies' ionization data by using the well-known Henderson-Hasselbalch equation that relates pH, pKa, and the log ratio of ionized and unionized portions of a molecule. (Tr. 162:14-164:4.)

DFF66. Admitted that a POSA could have generated such data, denied that it was done and published in the prior art. *See* DFF-65.

Defendants Finding No. 67. Cassidy further illustrates to a POSA that buprenorphine solubility increases exponentially as pH decreases from 5 to 4, which anticipates the pH ranges claimed in the patents. (JTX-248-0004, Figure 1; JTX-248-007-0008; Tr. 152:14-153:2, 153:9-20.)



(DDX 4-15.)

DFF67. Denied. *See* Resp. DFF57; PFF51-52.

Defendants Finding No. 68. As shown by the illustration, at a pH of about 5, about 1 mg/mL buprenorphine is soluble, but at a pH of about one unit less, i.e., at a pH of just above 4, about 10 mg/mL buprenorphine is soluble. (JTX-248-0004, Figure 1, JTX-248-0007-0008; Tr. 151:17-24.) Because the pH scale is logarithmic, a 10-fold increase in solubility per one unit drop of pH represents an exponential increase in solubility. (JTX-248-004, Figure 1, JTX-248-0007-0008; Tr. 151:17-24.)

DFF68. Denied. *See* Resp. DFF57; PFF51-52.

Defendants Finding No. 69. At acidic pH values, a one unit change in pH changes buprenorphine solubility by a factor of 10. (JTX-248-0004, Tr. 151:17-24.)

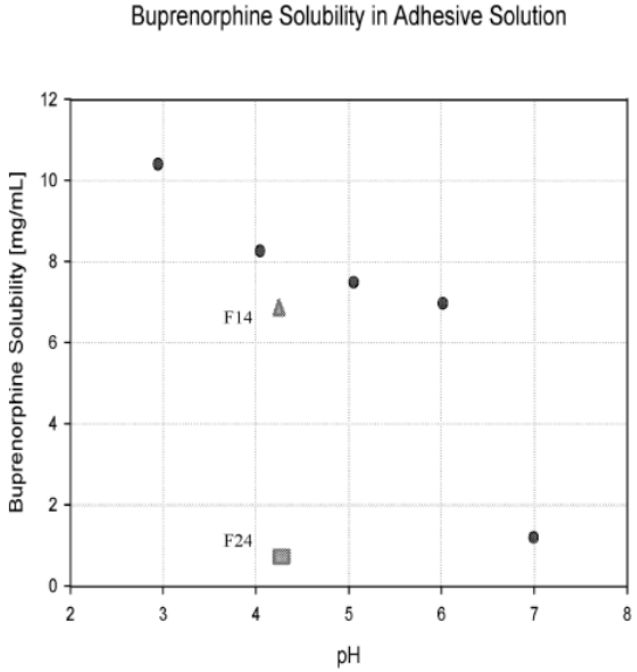
DFF69. Denied. *See* Resp. DFF-57; PFF-51-52.

Defendants Finding No. 70. A BDSI development report for BELBUCA cites Cassidy directly, and states "[a]s per the literature, the solubility of buprenorphine at approximately pH 7.8 is 100x less that the solubility of buprenorphine at a pH of approximately 5." (DTX-370-0018.) The development report reproduced Cassidy Figure 1, but does not include data

> relating to the outlier point at pH 4.2 for TPS buffer. (JTX-248-0004; Tr. 148:15-150:9, 680:17-681:23.) The development report states that the final BELBUCA product formulations (F14 and F24) were "formulated in the pH of highest [aqueous] solubility" as well as at concentrations lower than the solubility limit of the polymer system. (DTX-0370-0018-0019; JTX-248-0004; see Tr. 680:17-681:23.) (DTX-370-0019.) Dr. Williams confirmed that this reference to the highest aqueous solubility refers to Cassidy data. (Tr. 679:23-680:7.)

DFF70. Denied. Cassidy did not characterize the data point at pH 4.2 as an outlier. *See* JTX-248-0004. Cassidy was cited in the development report as a basis for comparison (DTX-370-0019), but the sentence cited by Defendants concerning BELBUCA pertains to the solubility of the novel polymeric diffusion environment of the mucoadhesive layer created by the inventors: "F14 and F24 [BELBUCA formulations] mucoadhesive blend formulations were formulated in the pH of highest solubility and at concentrations lower than the solubility limit ***as shown in Figure 7***." (DTX 370-0019 (emphasis added).) Figure 7, show below, is the solubility data for the mucoadhesive solution—not Cassidy. DTX 370-0020; JTX-248-0004. This was made clear during Dr. Williams testimony on re-direct. Tr.704:7-705:13.

Figure 7 Solubility of Buprenorphine HCl in the Mucoadhesive Solution (Courtesy LTS Lohmann Therapie Systems)



Defendants Finding No. 71. BDSI recognized the importance of the aqueous solubility of buprenorphine, as described by Cassidy, in formulating BELBUCA. (DTX-370-0019; JTX-248-004; Tr. 680:12-682:8.)

DFF71. Denied. *See* DFF70.

Defendants Finding No. 72. During manufacture, buprenorphine and the polymers dissolve in water, which is later removed during the drying process. (Tr. 674:19-675:7.) A POSA would know that in the final product, buprenorphine exists as a solid and must dissolve and ionize in the saliva in order to leave the dosage form and permeate the membrane. (Tr. 132:14-134:2, 701:6-702:23) The solubility of buprenorphine in the polymer casting solution is not relevant to the requirement that buprenorphine be soluble in saliva. (Tr. 201:14-19, 202:18-25, 701:6-702:5.)

DFF72. Denied. This finding misstates how the claimed invention works. *See* PFF23-28.

Defendants Finding No. 73. Weinberg teaches that buprenorphine has the highest partition coefficient (and is the most lipophilic) as compared to eight other known opioids. (JTX-249-0002, Table 1; Tr. 137:20-138:13.)

DFF73. Denied. Table 1 in Weinberg shows that buprenorphine has the highest partition coefficient. (JTX-249-0002.) Plaintiffs deny Dr. Michniak-Kohn characterization of this table and the data.

Defendants Finding No. 74. Because of its partition coefficient, which reflects its tendency to go into lipid environments of cell membranes, a POSA would have expected buprenorphine, in its fully ionized form, to permeate the lipid environment of the mucosal membrane. (Tr. 135:11-136:12, 136:18-24.)

DFF74. Denied. See PFF 46-50.

Defendants Finding No. 75. Weinberg reports that buprenorphine, at pH 6.5, where a POSA would have known buprenorphine to be nearly 100% ionized, absorbs well across the oral mucosa. (JTX-249-0006; Tr. 168:24-171:2.)

DFF75. Denied. *See* Resp. DFF65; PFF46-50. Further, Dr. Davies specifically testified that the nonionized form appears in significant amounts between pH values of about 6 and 12. (Tr.730:13-15, 734:9-13, 741:17-21).

Defendants Finding No. 76. Weinberg teaches that the poor solubility of buprenorphine at pH 6.5 prohibits the formulation of buprenorphine at higher, basic pH values. (JTX-249-0006; Tr. 170:10-22.)

DFF76. Denied. Weinberg merely states that it was having difficulty solubilizing buprenorphine in their liquid formulations at pH values higher than 6.5. JTX-249-0006; PFF55.

PFF55. The inventors were able to solubilize buprenorphine in their inventive formulation with a pH of 7.25, and obtain results better than Suboxone®. (Tr.762:21-763:9, 754:2-5, 755:7-10); JTX-001, Fig. 3; JTX-365-0004.

Defendants Finding No. 77. Todd states, "[b]uprenorphine is a potent antagonist analgesic with good bioavailability following sublingual administration, useful in the relief of moderate to severe pain and also in the treatment of narcotic addiction." (DTX-174-0001 at abstract; Tr. 173:18-174:6.)

DFF77. Admitted that this quote is in Todd. Plaintiffs deny that the Todd formulation actually had "good bioavailability." See PFF-45 below.

PFF56. While Todd's formulations might have good bioavailability when compared to oral, which is approximately 10%, a POSA as of 2006, would know that Todd's liquid formulations containing aqueous ethanol, had a bioavailability of about only 30%. PFF19.

Defendants Finding No. 78. Todd recognizes that "[b]uprenorphine effectively relieves moderate to severe pain in doses of 0.15 mg or more administered either parenterally or sublingually," and discloses that the "optimum therapeutic range" for buprenorphine sublingual tablets is 0.2 to 0.4 mg. (DTX-174-0002 at 1:9-14.)

DFF78. Denied. While Todd does say that the "optimum therapeutic range for single doses is 0.3-0.6mg by injection and 0.2 - 0.4mg for sublingual tablets," Todd describes only experimentation with a liquid formulation and describes no experimentation with sublingual tablets and reports no data for such

tablets. (DTX 174-0001.) Bullingham-II describes experiments with sublingual tablets. (PFF45.)

> Defendants Finding No. 79. Todd teaches aqueous solutions of buprenorphine for sublingual administration. (DTX-174-0001 at abstract.)
>
> DFF79. Admitted.
>
> Defendants Finding No. 80. Todd states, "We have now developed stable liquid compositions containing buprenorphine at a high concentration suitable for sublingual administration. According to the present invention there is provided a pharmaceutical composition for sublingual administration comprising buprenorphine or a non-toxic salt thereof dissolved in 20-30% v/v aqueous ethanol buffered to between pH 4.5 to 5.5 with 0.05 to 0.2 molar concentration of a buffering agent." (D.I. 249 at 2; see also DTX-174-0003-0004 at 2:21-3:4, Example 17.)
>
> DFF80. Admitted.
>
> Defendants Finding No. 81. Todd teaches a finite number of acidic pH values for its sublingual buprenorphine solutions, i.e., pH 4, 5, and 6, each of which provide "uptake," i.e., absorption, of buprenorphine that a POSA would have known was ~100% ionized. (DTX-174-0003 at 2:11-17; Tr. 174:12-175:25.)
>
> DFF81. Denied. *See* PFF57-63, below. Todd does not discuss the ionization states of buprenorphine. *See* Resp. DFF65.
>
> **PFF57.** The liquid formulation of Todd is a different than the solid polymeric devices of the claimed invention and also Moro and Tapolsky. (Tr.652:8-654:14.)
>
> **PFF58.** The pH range used in Todd was not for enhanced uptake but to address a different problem, solubility/stability. (Tr.653:22-654:2.)

PFF59. As Todd sought to make a liquid formulation that was designed to stay under the tongue for a period of time, it was essential that the buprenorphine stay in solution. (Tr.652:21-654:2.)

PFF60. Todd explained that it had difficulties keeping the buprenorphine stable and in solution. "We have found it very difficult to prepare stable aqueous solutions of adequate concentration for sublingual administration." (Tr.652:24-653:9; 265:21-266:2); DTX-174-0003.

PFF61. It is for these solubility/stability reasons that Todd lowered the pH of its formulation (from 4.5 to 5.5) to increase the solubility of buprenorphine, and also used 20-30% aqueous ethanol as a co-solvent to dissolve buprenorphine and keep it in solution, "[b]oth are required." (Tr.653:10-21; 265:15-24.)

PFF62. Todd states that it obtained higher uptake, using higher pH values of 5 and 6. (Tr.671:16-672:2, 733:12-734:13, 798:23-799:20); DTX 174-0003.

PFF63. Based on the above, a POSA reading Todd would not believe that lower pH ranges would enhance the uptake of buprenorphine. Rather, Todd is perfectly consistent with all the prior art discussed

above, which taught that increasing the pH of a weakly basic compound would increase absorption and bioavailability. PFF46-50.

Defendants Finding No. 82. Todd also includes 18 examples of buprenorphine formulations buffered to a pH between 4.5 and 5.5, including at a pH of 4.5, at a pH of 5, and at a pH of 5.5, where a POSA would have known buprenorphine to be 100% ionized. (DTX-174-0005-0007 at 4:5-6:19; Tr. 175:16-25, 671:16-672:7.)

DFF82. Denied. Todd does not discuss buprenorphine ionization states. *See* Resp. DFF65; PFF53-54, 57-63.

Defendants Finding No. 83. Citric acid/sodium citrate buffers, the same buffers used in BELBUCA, are disclosed by Todd and used in one of its examples. (DTX-174-0003-0004 at 2:21-3:4, DTX-174-0005 at Example 1, DTX-174-0007 at Example 17; Tr. 173:18-174:2.)

DFF83. Denied. The buffers in BELBUCA are "[m]onobasic sodium phosphate, sodium hydroxide, and citric acid." (DTX-019-0025.) The buffers used in example 1 of Todd are: "citric acid/disodium hydrogen phosphate buffer." (DTX-174-0005.)

Defendants Finding No. 84. Dr. Williams criticized Todd because the aqueous solutions utilize water and ethanol as co-solvents. (DTX-174-0003-0004 at 2:21-3:4; Tr. 173:18-174:2, 652:21-653:21.)

DFF84. Denied. Dr. Williams did not criticize anything. Dr. Williams correctly testified that Todd used aqueous ethanol as a solvent to solubilize the buprenorphine due to stability/solubility concerns. (Tr.652:8-653:21.)

Defendants Finding No. 85. However, Tapolsky teaches that its device preferably includes a combination of water and ethanol as solvents. (DTX-173-0009 at [0063].)

DFF85. Denied. Tapolsky-2005 stated: "[i]n one embodiment, the components are dissolved in a biocompatible solvent, preferably an aqueous medium." DTX-173, ¶63. Ethanol is not identified as a preferable solvent but only one that "may" used.

> Defendants Finding No. 86. The '866 and '843 patents also describe water as the solvent, and do not preclude the use of ethanol as a co-solvent. (JTX-001-0015 at Example 1, 19:21-22, 40-42, 018 at Example 3, 25:45-53.) Furthermore, the patents prefer ethanol as a disintegration aid that can be included in the claimed buprenorphine devices to "increase the disintegration rate and shorten the residence time of the device …." (JTX-001-0012 at 17:7-15; Tr. 672:8-674:1.)

DFF86. Denied. The '866 and '843 patents do not describe the use of ethanol as a solvent, as it is not required to solubilize the buprenorphine in the claimed polymeric diffusion environment. PFF51-52. Neither of the patents "prefer" ethanol as a disintegration aide, but say it could be used "optionally," and a "disintegration aid" to break up the device and help it bio-erode to reduce residence time. (JTX-001, col.17:7-9.) This has nothing to do with solubilizing buprenorphine.

> Defendants Finding No. 87. In 2002, FDA approved Suboxone® sublingual tablets. (JTX-471-0003; Tr. 480:12-82:2.)

DFF87. Admitted.

> Defendants Finding No. 88. As noted in the label, Suboxone® includes buprenorphine hydrochloride and pH buffers (citric acid/sodium citrate). (DTX-172-0002; Tr. 153:25-154:10, 160:17-25, 694:3-23.)

DFF88. Denied. DTX-172-0002 is "a part of the NDA for Suboxone®" that Defendants alleged was the label for Suboxone®. (Tr.100:3-11.) There is nothing that establishes that this portion of the NDA was publicly available to a POSA as of 2006. The document states that Suboxone® contains "citric acid and sodium citrate," but it does not say that they are used as buffers. Dr. Williams stated there are other uses for citric acid/sodium citrate other than buffers, and he did not say that Suboxone® was buffered, even knowing it possessed these two chemicals. (Tr.694:18-20, 699:9-14, 160:17-25.)

Defendants Finding No. 89. Citric acid/sodium citrate are the same buffers used in BELBUCA. (JTX-233-0023, Tr. 174:7-11, 694:21-23.)

DFF89. Denied. The buffers in BELBUCA are "[m]onobasic sodium phosphate, sodium hydroxide, and citric acid." DTX-019-0025; *See* Resp. DFF88.

Defendants Finding No. 90. A POSA would have understood the pH buffers in Suboxone® would reduce the pH of saliva to allow it to dissolve and ionize the buprenorphine. (Tr. 131:19-134:9, 160:17-25.)

DFF90. Denied. The cited pages are not referring to the working mechanism of Suboxone®.

Defendants Finding No. 91. BDSI submitted the Declaration of Dr. Maureen Reitman to the PTO in the context of an *Inter Partes* Review, where BDSI sought to establish the pH of Suboxone® in order to invalidate a competitor's patent. (DTX-365-0001, 0003.)

DFF91. Denied. DTX-365 does not support this finding. This finding is also irrelevant.

Defendants Finding No. 92. Following a simple, well-accepted procedure, Dr. Reitman determined that Suboxone® provides a pH of 3.5 in solution. (DTX-365-0003 at ¶¶ 4-5; Tr. 164:4-162:3; *see also* Tr. 695:19-696:2.)

DFF92. Denied. There was no "well-accepted procedure" as of 2006, or even today, to dissolve a Suboxone® tablet in water and measure its pH, and the amount of water used would affect the test. (Tr.703:9-704:6.)

Defendants Finding No. 93. To determine the pH, Dr. Reitman placed the tablet and a pH meter into deionized water and measured the pH of what was produced. (Tr. 161:15-23.)

DFF93. Denied. DTX-365 does not merely say use ionized water but provides specific amounts of 1.5ml and 3.0 ml. The unrebutted evidence at trial shows that this amount of water was not "standard" in 2006. *See* Resp. DFF92.

Defendants Finding No. 94. BDSI admitted to the PTO that the pH of Suboxone® was inherent to the tablets and known to be 3.5. *See* Petition, BioDelivery Sciences Int'l, Inc. v. RB Pharms. Ltd., IPR2014-00325, Paper 8 (PTAB filed Jan. 15, 2014), at pp. 6, 10.[3] According to BDSI, the pH "can be readily obtained in a matter of minutes by anyone with deionized water and a pH meter." (*Id.* at p. 42; *see also* Tr. 695:19-696:3.) n.3: This document is the publicly-available petition that BDSI submitted to the Patent Office, which attached the Reitman Declaration in support of a request for inter partes review of U.S. Patent No. 8,475,832. The document itself is not in evidence, but should be considered with the Reitman Declaration.

DFF94. Denied. Defendants have admitted that this unverified document was not entered into evidence. DFF94 should thus be stricken from Defendants' findings and post-trial brief.

Defendants Finding No. 95. The trial record demonstrates that a POSA would have understood that Suboxone®, at a pH of 3.5, provides

transmucosal absorption of 100% ionized buprenorphine. (DTX-365-0003 at ¶ 5; DTX-172-0004; Tr. 154:11-16, 160:17-162:3, 167:18-168:23.)

DFF95. Denied. *See* Resp. DFF65; PFF40-41.

PFF64. A POSA in 2006 would know that Suboxone® had a bioavailability of about 25%. PFF21.

PFF65. There was no consensus, even as late as 2014, as to whether Suboxone was effective in treating chronic pain. (Tr.528:18-531:19, 538:20-539:3); JTX-229-0001, 0006.

PFF66. There are no published studies showing that Suboxone works for the treatment of chronic pain. *Id*.

PFF67. Suboxone was not approved for the treatment of chronic pain, and even today, is not so approved. (Tr.521:25-522:13.)

PFF68. Suboxone is approved for opioid dependence. *Id*.

PFF69. The highest dose of Suboxone® is some four times higher than the highest dose of BELBUCA. (Tr.891:23-892:1.)

Defendants Finding No. 96. Birch discloses aqueous buprenorphine solutions, which can "induce rapid and prolonged analgesia when delivered intranasally to a patient." (DTX-203-0001 at abstract.)

DFF96. Denied. Defendants' characterization is incomplete. Birch describes formulations that are "suitable for intranasal administration" and contains excipients for nasal delivery. DTX-203-0001. Birch also has no relevance to the

oral transmucosal devices at issue in this case, or the enhanced uptake of such devices, and Defendants have not presented any evidence to the contrary.

Defendants Finding No. 97. The solutions have a pH between 3 and 4.8, where a POSA would have understood buprenorphine to be 100% ionized, and provide "rapid uptake" of buprenorphine across the nasal mucosa into the plasma. (DTX-203 at [0010]-[0021], [0071], [0083]; Tr. 171:3-172:22.)

DFF97. Denied. Birch does not discuss ionization states of buprenorphine. *See* Resp. DFF65, 96.

Defendants Finding No. 98. The BEMA delivery device of Tapolsky satisfies all requirements of claims 3 and 10 of the '866 patent, and claims 8, 9, and 20 of the '843 patent, except that Tapolsky does not disclose buprenorphine, and does not disclose that the polymeric diffusion environment is buffered to the claimed pH ranges. (Tr. 109:22-110:17.)

DFF98. Denied. *See* Resp. DFF1; PFF1-14.

Defendants Finding No. 99. BDSI did not offer any contrary testimony regarding the disclosure of Tapolsky. (Tr. 650:22-652:7.)

DFF99. Denied. *See* Resp. DFF1; PFF1-14. Further, it is Defendants' burden to show obviousness in view of the prior art.

Defendants Finding No. 100. A POSA would have been motivated to use buprenorphine in Tapolsky's BEMA platform because of the known properties of buprenorphine, and because the prior art taught its formulation in a BEMA device for buccal delivery. (Tr. 112:16-23, 129:23-130:19; see also Tr. 109:12-110:17, 247:13-16, 247:25-248:16.)

DFF100. Denied. The entirety of the prior art demonstrates that there was no such motivation. *See e.g.* (Tr.653:22-654:18); PFF1-14; Resp. DFF1.

Defendants Finding No. 101. Johnson teaches that buprenorphine has been available as a parenteral and sublingual analgesic since the 1970s, and "has been found to be amenable to new formulation technology based on its

physiochemical and pharmacological profile." (DTX-165-0001; Tr. 96:15-25; see D.I. 249 at 5.)

DFF101. Admitted.

Defendants Finding No. 102. Cassidy taught that buprenorphine is 20-40 times more potent than morphine. (JTX-248-0001; Tr. 94:20-25, 99:11-15; see D.I. 249 at 4.) Cassidy recognized that buprenorphine has high first pass effect but suggested that buccal delivery "offers advantages in terms of accessibility" while providing "the ability to provide controlled delivery for extended periods of time." (JTX-248-0001; Tr. 94:20-96:2.) A POSA would have known that "administration of an analgesic at a constant rate results in both optimal patient comfort and a reduced total amount of analgesic," such that "[c]ontrolled delivery of buprenorphine may, therefore, offer advantages in pain management." (JTX-248-0001; Tr. 94:20-96:2.)

DFF102. Denied. *See* Resp. DFF57; PFF51-52. By 2005, it was known that buccal strips had poor bioavailability. DTX-165-0007, Fig. 3. PFF20. Further, the cited testimony does not support this finding.

Defendants Finding No. 103. At trial, BDSI agreed that Cassidy teaches that buprenorphine is 20-40 times more potent than morphine and has a high first pass effect. (DDX4-5; Tr. 143:12-13; see also D.I. 249 at 4.)

DFF103. Admitted

Defendants Finding No. 104. A POSA would have known from Johnson, Bullingham I, and Cassidy that buprenorphine is a potent opioid analgesic that is highly lipophilic, meaning it absorbs well even in ionized form, and experiences high first pass effect requiring transmucosal or other delivery that avoids liver metabolism. (DTX-165-0001-0003, 0005, 0008-0009; Tr. 96:4-98:22, 485:1-487:1; DTX-077-0001, 0005; Tr. 91:2-19, 93:25-94:9; JTX-248-0001-0002; Tr. 94:16-96:2.)

DFF104. Denied. The prior art showed that buprenorphine was *not* absorbed "well" and buprenorphine formulations, other than intravenous or injection, had poor bioavailability. PFF18-22; DTX-165-0006-0007, Fig. 3. None

of Johnson (DTX-165), Bullingham-I (DTX-077, or Cassidy (JTX-248) discusses ionization. *See* Resp. DFF65.

> DEFENDANTS FINDING NO. 105. A POSA also would have known from Johnson, Bullingham I, and Cassidy that the oral transmucosal administration of buprenorphine provides an effective, convenient delivery route that avoids the first pass effect. (DTX-077-0001,0005; JTX-248-0001; DTX-165-0002; Tr. 91:10-19, 92:14-18, 93:8-13, 94:20-95:16, 99:11-15.)

DFF105. Denied. Buprenorphine was not shown to be effective for chronic pain in the Unites States as of 2006. *See* PFF 15-16. Even today, there are no studies showing Suboxone® works to treat chronic pain. *See* PFF65-66. Buccal and sublingual formulation of buprenorphine as of 2006 were plagued by low bioavailability. *See* Resp. DFF104; PFF 18-21.

> Defendants Finding No. 106. Cassidy teaches that buccal devices could improve bioavailability by providing unidirectional delivery that avoids loss due to swallowing. (JTX-248-0001; Tr. 95:10-13.)

DFF106. Denied. Cassidy (1993) theorizes about using a device with an impermeable backing layer, which is entirely different from the bioerodible devices of the patents-in-suit. (JTX-001, claim 1.) Cassidy uses two formulations— non-woven and hydrogel—which are not taught by the patents-in-suit. (Tr.269:9-17.)

> **PFF70.** There were no commercially available buccal two-layer films delivering buprenorphine before BELBUCA, which first became available in 2016.

Defendants Finding No. 107. Yang, Chen and Das illustrate the broad application of the BEMA platform to opioids like buprenorphine.[4] (DTX-175 at [0014], [0131]; DTX-176-0005-0006, 0008; DTX-323-0003; Tr. 123:14-124:3, 124:4-125:8, 128:16-129:22.) n.4: Yang, Chen, and Das published prior to July 21, 2006, the earliest possible filing date of the '866 and '843 patents. (DTX-175-0001; DTX-176-0001; DTX-323-0001.)

DFF107. Denied. The cited testimony does not substantiate the assertion that Yang, Chen and Das illustrate a "BEMA platform" or its "broad application" to opioids. *See* Resp. DFF1; PFF71-75.

Defendants Finding No. 108. Yang discloses mucoadhesive polymeric "rapid dissolve film products" for the transmucosal administration of opioids, which can include buffers. (DTX-175 at [0014], [0131], [0133], [0161], [0209]-[0210]; Tr. 128:16-129:22.)

DFF108. Denied. See PFF 71-75.

PFF71. Yang teaches that historically, using films as drug delivery systems have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice. (Tr.275:3-11.)

PFF72."Yang does not teach an example of the use of any opioid in any device." (Tr.276:8-10.)

PFF73. Yang does not teach any plasma concentrations of buprenorphine. (Tr.275:24-276:1.)

PFF74. Yang does not teach any pH values for any mucoadhesive layer, nor does it teach buffering the pH of a polymeric diffusion environment. (Tr.276:2-7, 11-13.)

PFF75. Yang does not teach any pH values for any backing or barrier layer. (Tr.276:5-7.)

Defendants Finding No. 109. Chen teaches a mucoadhesive film including an effective amount of a drug, such as an opiate like hydromorphone, dispersed in a polymeric diffusion environment. (DTX-176-0005-0006, 0008; Tr. 124:4-125:88.)

DFF109. Denied. The cited testimony does not support the proposed finding. "Chen was interested in Sildenafil." (Tr.272:12-14); *See* DFF 76-80.

PFF76. Chen discloses an effective dose of Sildenafil citrate formed into a solid dispersion with Xylitol to treat erectile dysfunction. (Tr.272:18-21.)

PFF77. Chen was not interested buprenorphine. (Tr.272:12-14.)

PFF78. Chen does not teach any plasma concentrations of buprenorphine. (Tr.273:11-13.)

PFF79. Chen does not teach any device having a backing or barrier layer. (Tr.273:14-16.)

PFF80. Chen does not teach any pH values for any mucoadhesive layer. (Tr.273:17-19.)

Defendants Finding No. 110. Das predicted that the use of a "mucoadhesive delivery system" for buprenorphine would improve its bioavailability, and describes mucoadhesive tablets and films for sublingual delivery. (DTX-323-0003; Tr. 123:14-124:3.)

DFF110. Denied. *See* PFF81-87.

PFF81. Das teaches away from the inventions claimed in the patents-in-suit. "Das concludes that the mucoadhesive tablet formulations produced overall superior results compared with the mucoadhesive film formulations." (Tr.270:3-6); DTX323-0007.

PFF82. Das further teaches away, explaining that mucoadhesive polymer film formulations without plasticizers are not suitable for industrial scaleup. (Tr.271:3-8); DTX323-0004.

PFF83. Das teaches that studies on buprenorphine drug delivery systems are relatively few. (Tr.270:11-13.)

PFF84. Das does not teach any plasma concentrations of buprenorphine. (Tr.271:22-24.)

PFF85. Das does not teach any pH values for a mucoadhesive layer. (Tr.271:25-272:2.)

PFF86. Das does not teach any pH values for a backing or barrier layer. (Tr.272:3-5.)

PFF87. Das does not provide any data demonstrating an enhanced uptake of any pharmaceutical ingredient. (Tr.272:6-8.)

Defendants Finding No. 111. POSAs believed that a "mucoadhesive delivery system" generally, and BEMA films specifically, could improve bioavailability over sublingual tablets by providing unidirectional delivery that avoids loss due to swallowing. (JTX-248-0001; DTX-323-0003; Tr. 95:10-13.)

DFF111. Denied. *See* DFF1, PFF1-14, 81. The cited testimony does not substantiate this assertion; it does not contain a discussion regarding "BEMA films specifically." Rather, it contains Dr. Michniak-Kohn's opinions regarding proposed advantages of buccal delivery. Further, Dr. Michniak-Kohn is discussing Johnson (DTX-165)—not Cassidy (JTX-248) and Das (DTX-323).

> Defendants Finding No. 112. Tapolsky and Moro teach that BEMA devices can transmucosally deliver opioids generally, and Moro teaches buprenorphine specifically. (DTX-173 at [0046]-[0053]; DTX-362-001 at abstract; DTX-178 at [0035], [0046], [0048], [0064]; Tr. 110:18-112:1, 112:16-23, 121:9-17, 117:22-118:11, 118:12-22, 120:13-16, 129:23-130:19, 261:4-262:3.)

DFF112. Denied. *See* Resp. DFF1; PFF1-14, 29-36.

> Defendants Finding No. 113. Known therapeutic ranges for buprenorphine were 300-600 μg for injection and 200-400 μg for sublingual tablets. (DTX-174-0002 at 1:12-14; DTX-165-0020; Tr. 134:3-5.)

DFF113. Denied. Trial testimony does not substantiate this assertion. The cited portion of the transcript provides the following from Dr. Michniak-Kohn: "Again, literature publishes, basic knowledge. You would be able to achieve the delivery of buprenorphine in adequate amounts to treat chronic pain." Furthermore, Dr. Michniak-Kohn was providing her explanation for "how BEMA devices" work in this answer, which does not include any specific reference to Todd (DTX-174) or Johnson (DTX-165).

> Defendants Finding No. 114. Providing an effective amount of an opioid like buprenorphine in the BEMA devices of Tapolsky or Moro would have

been a matter of routine skill. (DTX-173 at [0034], [0054]; Tr. 129:23-130:19, 131:19-23,134:3-5.)

DFF114. Denied. As explained above, Tapolsky-2005 and Moro do not teach BEMA devices. *See* Resp. DFF1; PFF1-14, 29-36. Further, none of the Defendants' citations concern Moro.

Defendants Finding No. 115. Claims 3 and 9 of the '866 patent are directed to Tapolsky's BEMA device containing buprenorphine buffered to a pH "between about 4.5 and about 5." (JTX-001-0012, 019 at 13:1-4, claim 3, claim 9.) Claims 8, 9 and 20 of the '843 patent are directed to Tapolsky's BEMA device containing buprenorphine buffered to a pH "between about 4 and about 6." (JTX-002-0014, 0021 at 13:26-32, claim 8, claim 9, claim 20.)

DFF115. Denied. *See* Resp. DFF1, PFF1-14. Claim 9 of the '866 patent was not asserted at trial. Claim 9 of the '843 patent contains a buffered polymeric diffusion environment buffered to between about 4 and about 7.5.

Defendants Finding No. 116. "Basic science" and common sense dictate that buprenorphine must dissolve from the BEMA device into the saliva before it can permeate the mucosa. (Tr. 132:14-134:2, 701:13-702:5.) Dr. Williams acknowledged this fact. (Tr. 701:13-702:5.)

DFF116. Denied. *See* PFF23-28.

Defendants Finding No. 117. Dr. Williams testified that buprenorphine is a BCS-II drug, and that a POSA would have known that buprenorphine would absorb across the mucosa if dissolved and ionized—such as in saliva buffered to a pH between 4 and 5. (Tr. 699:18-700:4.)

DFF117. Denied. *See* PFF23-28, 37.

Defendants Finding No. 118. There is no dispute that the solubilization of buprenorphine from a BEMA device is highly pH dependent. (Tr. 133:2-6, 133:15-21, 146:6-12, 689:21-690:7.)

DFF118. Denied. The cited portion of Dr. Williams' testimony, states that "the dissolution of buprenorphine from these films is pH dependent." (Tr. 689:21-690:7.) Further, part of the cited testimony of Dr. Michniak-Kohn states that "the process of dissolution and ionization are highly influenced by pH." (Tr.146:6-12.) The issue of dissolution is not relevant to this case. Further, as discussed above, buprenorphine is already solubilized in the claimed device and does not need to dissolve in saliva. *See* PFF23-28.

Defendants Finding No. 119. In addition, there is no dispute that buprenorphine must ionize in order to dissolve, and its ionization is likewise highly pH dependent. (Tr. 146:6-12; 670:6-20; 671:16-674:1.)

DFF119. Denied. *See* PFF23-28.

Defendants Finding No. 120. The dissolved and ionized buprenorphine then moves through the mucoadhesive layer by concentration gradient and permeates the mucosal surface, where it is absorbed into the bloodstream. (Tr. 132:22-133:14.) A POSA would have known that buprenorphine has to be dissolved to be able to permeate the mucosa. (Tr. 132:22-133:6.)

DFF120. Denied. *See* PFF23-28.

Defendants Finding No. 121. Cassidy shows that the solubility of buprenorphine is highly pH-dependent and increases exponentially as pH drops from 5 to 4, where it remains 100% ionized. (JTX-248-0004, Figure 1; Tr. 147:7-23, 151:17-24; DTX-377-0002, 0004; Tr. 162:14-164:19; 165:21-166:11.)

DFF121. Denied. *See* Resp. DFF57, PFF51-52.

PFF88. The data in Cassidy for lower pH values may not be reliable. (Tr.268:14-16.)

PFF89. Cassidy teaches two formulations— non-woven and hydrogel—which are not taught in the patents-in-suit. (Tr.269:9-17.)

PFF90. Cassidy does not teach the use of any backing layer. (Tr.269:18-20.)

PFF91. Cassidy does not teach any human pharmacokinetic data. (Tr.269:21-23.)

Defendants Finding No. 122. Cassidy shows that the solubility of buprenorphine is highly pH-dependent and increases exponentially as pH drops from 5 to 4, where it remains 100% ionized. (JTX-248-0004, Figure 1; Tr. 147:7-23, 151:17-24; DTX-377-0002, 0004; Tr. 162:14-164:19; 165:21-166:11.)

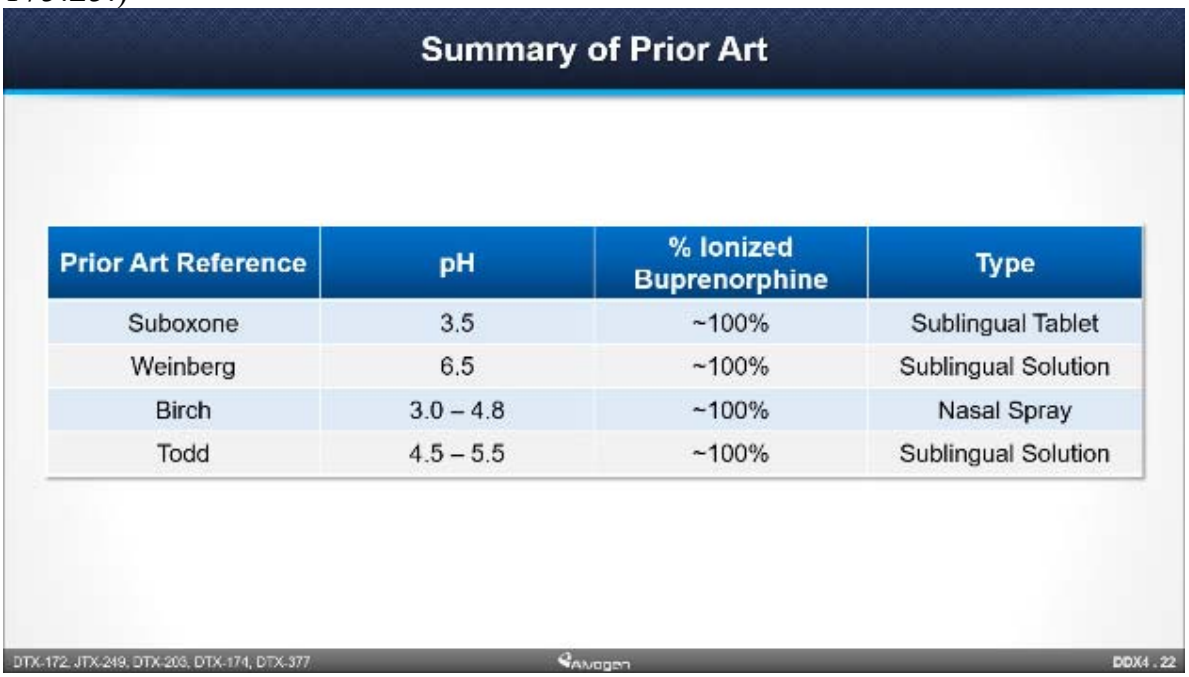
DFF122. Denied. DFF57, 65; PFF51-55, 88-91.

Defendants Finding No. 123. A POSA would have expected that a polymeric diffusion environment of Tapolsky buffered to a pH around these values would provide the highest amount of dissolved and ionized buprenorphine to be available for absorption. (Tr. 146:6-12, 153:9-20, 166:12-23.) Thus, a POSA would have buffered the polymeric diffusion environment of Tapolsky's device to acidic pH values with a reasonable expectation of optimizing the transmucosal absorption of buprenorphine. (Tr. 200:22-201:13.)

DFF123. Denied. The entire trial record shows that this is not the case. *See* Resp. DFF57, PFF23-28, PFF46-52. This also mischaracterizes the claimed invention, which is to obtain enhanced uptake, which the inventors unexpectedly accomplished. *See* PFF12.

Defendants Finding No. 124. The prior art corroborates this expectation – pH values of 3-4.8 (Birch), 3.5 (Suboxone®), 4-5 (Cassidy), 4- 6 (Todd), and 6.5 (Weinberg). Regardless of dosage form, prior art transmucosal

formulations provide buprenorphine at acidic pH where it is dissolved and ~100% ionized, and demonstrate its absorption. (JTX-249-0006; DTX-174-0003 at 2:11-17; DTX-377-0002, 0004; DTX-365-0003 at ¶ 5; DTX-365-0003 at ¶ 5; DTX-203 at [0010]-[0021], [0071], [0083]; Tr. 154:11-16, 160:17-162:3, 162:14-164:19; 165:21-166:11; 167:18-172:22, 174:12-175:25.)



(DDX 4-22.) Therefore, the prior art confirms that a POSA would have expected dissolved and ionized buprenorphine to readily permeate mucosal membranes at these acidic pH values.

DFF124. Denied. *See* Resp. DFF57, 65, PFF23-28, 46-52. Further, that buprenorphine formulations were absorbed in the prior art at some low level is not the claimed invention, which are oral transmucosal formulations that provide *enhanced uptake*, as measured by bioavailability and plasma concentration. *See e.g.*, JTX-001-0001, 0006, 0007, 0018, claim 1. The oral transmucosal formulations of the prior art had poor bioavailability. *See Resp.* DFF10; PFF18-21.

Defendants Finding No. 125. Dr. Williams agreed that Todd, for example, taught a POSA that buprenorphine absorbs transmucosally at acidic pH values where it is ~100% ionized. (Tr. 671:16-674:1.)

DFF125. Denied. Todd does not describe ionization conditions. *See* Resp. DFF65; DTX-0174. Dr. Williams was not asked whether the ionization states of buprenorphine were known as of 2006. Further, Todd used acidic pH values for the purpose of getting buprenorphine to solubilize, not to enhance uptake. PFF58-61. Todd was also forced to use aqueous ethanol to solubilize the buprenorphine. PFF61.

Defendants Finding No. 126. Because the pH of saliva varies from 5.8 to around 7, which is not ideal for dissolving buprenorphine, a POSA would provide buffers in the polymeric diffusion environment that dissolve in and acidify the saliva. (Tr. 153:9-24.)

DFF126. Denied. *See* PFF23-28.

Defendants Finding No. 127. The prior art taught that buffer systems maintain active agents in their ionized form to help "overcome the influence of the conditions of the surrounding environment, such as rate of saliva secretion, pH of the saliva, and other factors." (JTX-462 at [0057], Table 5; Tr. 153:3-8, 173:18-174:11.)

DFF127. Denied. *See* PFF23-28.

Defendants Finding No. 128. POSAs knew how to buffer transmucosal formulations of buprenorphine for this purpose. (Tr. 173:18-174:11.) For example, both Todd and Suboxone® include citric acid/sodium citrate buffers – the same buffers that are in Belbuca.® (DTX-174-003-004 at 2:21-3:4, Example 1, Example 17; DTX-172-0002, 0024; Tr. 153:25-154:10, 160:17-25, 173:18-174:2, 174:7-11, 694:3-23.) Just as BDSI did for BELBUCA, a POSA would have copied the acidifying buffers of Todd and Suboxone® in formulating Tapolsky's BEMA device for buprenorphine delivery. (Tr. 153:25-154:10, 160:17-25, 200:22-201:13.)

DFF128. Denied. *See* Resp. DFF1, PFF1-14. Buprenorphine is already solubilized in them mucoadhesive layer of the claimed invention. Resp. DFF38;

PFF23-28, 52. The liquid formulations relied on by Defendants are not applicable to the claimed solid film devise. Tr.653:22-655:8; PFF23-28, 57-63, 51-52; *see also* Resp. DFF57. Defendants also mischaracterize the teachings of the alleged Suboxone® label. *See* Resp. DFF88. There is nothing in the record that shows BDSI copied the acidifying buffers of Todd and Suboxone®.

> Defendants Finding No. 129. In view of the transmucosal formulations of Suboxone® and Todd, a POSA would have reasonably expected to use a citric acid/sodium citrate buffer in the polymeric diffusion environment of Tapolsky's device to maintain an acidic environment at the oral mucosa during bioerosion of the device. (Tr. 200:22-201:13.)

DFF129. Denied. *See* Resp. DFF1; PFF1-14, 23-28. Todd used a low pH range for solubility/stability. PFF57-63. In the claimed inventions, buprenorphine is already solubilized in the mucoadhesive layer and the point of the invention is to enhance uptake. *See e.g.,* JTX-001-0001, 0006, 0007, 0018, claim 1; Resp. DFF38; PFF52. The prior art oral transmucosal formulations had poor bioavailability. PFF18-21; *see* Resp. DFF10. Moreover, it was known that for weakly basic drugs—e.g., buprenorphine—that absorption increased with an increase in pH, where the drug was predominately in its unionized form. PFF46-50. The inventors unexpectedly found that lower pH values enhanced bioavailability. PFF12.

> Defendants Finding No. 130. Todd would have provided a POSA with a reasonable expectation of successfully delivering buprenorphine from Tapolsky's device having a polymeric diffusion environment buffered to an

acidic pH of about 4, about 5, or about 6, and from a pH of about 4.5-5.5. (Tr. 174:12-175:2.)

DFF130. Denied. *See* Resp. DFF128-29.

Defendants Finding No. 131. The '866 and '843 patents describe several opioids that can be used in the invention, including fentanyl, buprenorphine, and butorphanol. (JTX-001 at 9:54-67; JTX-002 at 10:5-24; Tr. 683:4-684:18.)

DFF131. Denied. The claims are limited to buprenorphine. E.g., JTX-001 at claim 1.

Defendants Finding No. 132. Dr. Williams testified that the '866 and '843 patents provide sufficient direction for a POSA to determine the optimal pH range for any of the opioids disclosed, even though the patents do not include a specific pH teaching for any opioids other than buprenorphine and fentanyl. (JTX-001-0011 at 11:49-12:10; JTX-002-0013 at 12:5-33; Tr. 684:19-685:12, 685:16-686:10.)

DFF132. Denied. Defendants mischaracterize Dr. Williams' testimony. Dr. Williams testified that the patents give a POSA "the tools as to . . . how to conduct the assessment to see if the pH within the range that's described in the patent, whether it would lead to enhanced absorption or not." (Tr.685:22-686:5.)

Defendants Finding No. 133. The time to first measurable concentration (i.e., Tfirst) in claim 4 and the duration of effective buprenorphine concentration in claim 5 are inherent properties of the device and dose administered as well as the sensitivity of the assay used to measure plasma concentration. (Tr. 327:12-328:12.)

DFF133. Denied. This finding does not indicate what "device" it is referring to and is vague. The cited testimony does not support the proposed

finding, and for example, is silent about the assertion that claims 4 and 5 are "inherent properties."

> Defendants Finding No. 134. In view of Bullingham I, a POSA would have reasonably expected achieving a Tfirst of about 45 minutes by administering buprenorphine in Tapolsky's BEMA device. (Tr. 343:16-344:1.)

DFF134. Denied. A POSA would not have had such a reasonable expectation. (Tr.807:18-809:25, 810:21-822:14); *See* Resp. DFF1; PFF37-42. Indeed, Dr. Shafer admitted that Bullingham-I does not provide buprenorphine plasma concentrations at 45 minutes. (Tr.403:11-13.)

> Defendants Finding No. 135. A POSA would understand that buprenorphine can be administered using Tapolsky's BEMA device to maintain an effective concentration of at least 4 hours. DTX-173, Table 5; Tr. 346:2-14.

DFF135. Denied. *See* Resp. DFF1. A POSA would not have had such an understanding. (Tr.807:18-25, 810:1-810:20); PFF43-45.

> Defendants Finding No. 136. The buprenorphine concentration-related parameters recited in claims 4 and 5 are not described in the '866 patent as providing any particular benefit, much less an unexpected result, when buprenorphine is administered transmucosally according to claim 1. (*See generally* JTX-001.)

DFF136. Denied. The '866 patent cites the values in Table 4, which include the pharmacokinetic parameters in claims 4 and 5, and states that "[a]s demonstrated in Table 4, the delivery device of the present invention at pH 6 appeared to provide enhanced uptake . . . ." JTX-001, col.25:64-66.

Defendants Finding No. 137. In Table 4 of the '866 patent, the Tfirst for buprenorphine is 45 minutes for devices having a pH of 6 that are within the scope of claim 1 allegedly providing an enhanced uptake as well as devices having a pH of 7.25 that are outside the scope of claim 1. (JTX-001-0018 at 25:64-26:10.)

DFF137. Denied. Plaintiffs do not understand this finding and thus deny it. The T_{first} for the device with the polymeric diffusion environment of a pH of 6 is 45 minutes. JTX-001, Table 4.

Defendants Finding No. 138. The '866 patent does not describe any benefit in maintaining buprenorphine concentrations effective for pain relief for at least 4 hours in contrast to shorter time periods. (JTX-001-0009 at 7:67-8:5.)

DFF138. Denied. The '866 patent describes the treatment of various types of pain, including chronic pain and acute pain. JTX-001-col.4:55-5:16. Defendants have presented no evidence that all such pain conditions last less than four hours.

Defendants Finding No. 139. During prosecution, the Examiner specifically rejected claims 4-5 in several Office Actions. (JTX-004-0211-0213; JTX-004-0260-0262; JTX-0004-0303-0305.)

DFF139. Admitted. This finding is irrelevant as the Examiner ultimately allowed the claims to issue, which are presumed valid.

Defendants Finding No. 140. In response, BDSI did not separately argue patentability based on the limitations in these claims. (JTX-004-0231-0234; JTX-004-0281-0285; JTX-004-0315-0322; JTX-004-0330.)

DFF140. Denied. Claims 4 and 5 contain the pH limitations that are in Claim 1 of the '866 patent. The pH limitations were sufficient to distinguish the

claims over the prior art, including Moro and Guo. JTX-004-0341. Nothing else was required.

Defendants Finding No. 141. In a petition for accelerated examination in the '866 patent, BDSI told the PTO that Tapolsky does "not teach administration of an opioid" (JTX-004-0033.) This is incorrect. Tapolsky teaches the administration of the opioid butorphanol as suitable for use in the BEMA platform. (DTX-173 at [0053], Tr. 112:16-23, 693:1-694:2.) Butorphanol is also listed in the specification of the '866 patent. (JTX-001 9:54-10:6; Tr. 112:5-15.)

DFF141. Denied. *See* Resp. DFF19.

Defendants Finding No. 142. During prosecution of the '866 patent, BDSI submitted the Declaration of Dr. Andrew Finn signed September 12, 2011 (the "Finn Declaration"). (JTX-004-0231-36.)

DFF142. Admitted

Defendants Finding No. 143. The Finn Declaration states, "the devices which include a polymeric diffusion environment which is a buffered environment having a pH of between 4 and about 6 exhibit dramatically improved Cmax and/or bioavailability as compared to devices having a polymeric diffusion environment at a pH of 7.25 or those having no buffered environment[.]" (JTX-004-0234.) Table 1 of the Finn Declaration sets forth the pharmacokinetic data for the devices that include a polymeric diffusion environment, and for Suboxone®. (JTX-004-0233-0234.)

DFF143. Admitted.

Defendants Finding No. 144. The Finn Declaration states that the increased bioavailability at lower pH values was "unexpected and could not have been predicted from a mere change in pH [.]" (JTX-004-0234.)

DFF144. Denied. The Finn Declaration states: "Such enhanced bio-availability *in the bioerodable device described in the present invention* was

unexpected and could not have been predicted from a mere change in pH or adhesive capability." JTX-365-0004 (emphasis added).

> Defendants Finding No. 145. Given that the solubility of buprenorphine was known to exponentially increase as pH drops from about 5 to about 4, and was lower at higher pH values, it was not surprising that the Cmax and bioavailability of buprenorphine would also increase for formulations in that pH range. (Tr. 182:14-183:17.) This is confirmed by a development report submitted to FDA in connection with the BELBUCA New Drug Application, which states, "[b]ased on buprenorphine pKa (8.5) and solubility data (solubility decreases as pH increases), the results for both film strengths in pH 6.8 dissolution media are low *as expected*." (DTX-024-0016; Tr. 687:17-688:14, 692:3-20) (emphasis added).

DFF145. Denied. Cassidy's data in aqueous environments is not applicable to the claimed polymeric diffusion environment. PFF51-52; Resp. DFF57. Further, Cassidy does not teach anything about enhanced uptake, as measured by bioavailability or C_{max} in humans. PFF91. The buprenorphine formulations in the prior art at low pH values were soluble, but also had poor bioavailability. *See* Resp. DFF10; PFF18-21. Further, the chart produced at DTX-024 is from dissolution studies of the *entire film* in different *liquid buffer solutions* conducted by Endo *in 2014*, for quality control purposes. DTX-024-00015-16. Such studies have nothing to do with the operation of the invention in actual use or the enhanced bioavailability from the mucoadhesive layer. PFF23-28.

> Defendants Finding No. 146. The Finn Declaration states that Suboxone® was not buffered. (JTX-0004-233, Tr. 181:24-182:21.) However, Suboxone® contains a citric acid-sodium citrate buffer as also utilized in BEMA films. (JTX-0004-233, DTX-172-2; Tr. 153:25-154:10, 694:3-23, 698:6-699:17.) The Finn Declaration also incorrectly states that the pH of

Suboxone® is "N/A". (JTX-0004-234, *see* DTX-365-003 at ¶¶ 4-5; Tr. 161:4-162:1; *see also* Tr. 693:18-694:1.)

DFF146. Denied. Dr. Williams explained that just because Suboxone® has citric acid and sodium citrate, this does not mean it is buffered. (Tr.694:20; 699:9-14.) Further, Defendants' allegations about the Suboxone® label are incorrect. *See* Resp. DFF88. And, as testified by Dr. Williams, that Suboxone® was or was not buffered has no impact on the unexpected data set forth in the chart. (Tr.702:21-703:-8.)

Dr. Finn's declaration correctly indicted the pH of Suboxone was "N/A." Finn's declaration was dated in 2011 and the study comparing BEMA devices 1 and 2 with Suboxone® were performed in 2006. JTX-352-0002. There is nothing in the literature as of 2006 or 2011 that states the pH of Suboxone®. The Reitman declaration, upon which Defendants rely, was created in 2014. DTX-365. Further, Dr. Williams offered unrebutted testimony that there was no standard technique for dissolving a tablet in water to determine its pH in either the prior art or today and that the amount of water used in the test would affect the results. (Tr.703:9-704:6.) The pH of the of Suboxone® tablets was not in the prior art.

Defendants Finding No. 147. In Table 1 of the Finn Declaration, the pH of the BEMA 1 formulation is listed as 7.25 and the pH of the BEMA 2 formulation is listed as 6.0. However, the actual pH of BEMA 1 was 6.8 and the actual pH of BEMA 2 is 5.3, as confirmed by a document in BDSI's NDA for BELBUCA provided to FDA. (DTX-024-0006; Tr. 183:22-184:8, 192:12-193:7, 687:17-688:14.)

DFF147. Denied. This finding cites to part of the NDA submitted by Endo Pharmaceuticals in 2014 (DTX-024), not BSDI. There is no explanation for when or how Endo came up with these numbers or whether they were obtained under similar conditions. (Tr.290:13-20.) Study BUP-101, which was conducted in 2006, specified the pH of BEMA 1 and BEMA 2, and reported that the pH values were 7.25 and 6.0, just as set forth in the declaration. *See e.g.*, JTX 352-0011, 0013, 0014, 0015, 00022, 0024, 0027. Dr. Finn specifically testified that the number for BEMA 1 and 2 in his declaration came from the BUP-101 study. (Tr.772:7-772:14.) And BDSI's version of the pharmaceutical development report, also signed, reviewed, and approved, by Endo personnel, describes the pH of the first two formulations as 7.25 and 6. DTX 019-0003, 0027.

> Defendants Finding No. 148. Dr. Williams testified that the developers of BELBUCA referred to the Cassidy reference when they were determining the solubility of buprenorphine. (Tr. 680:12-16.)

DFF148. Denied. Dr. Williams testified that "when the developers of Belbuca were determining solubility of buprenorphine in aqueous buffers, they referred to the Cassidy reference." (Tr.680:12-16.) This is not akin to the solubility in a polymeric diffusion environment. (Tr.624:6-11); *see* Resp. DFF70.

> Defendants Finding No. 149. BEMA 1 and BEMA 2 were the only formulations tested prior to the filing date of the '866 patent and were discussed in Example 4 (with data presented in Table 4). The data for BEMA 3-7, as presented in the Finn Declaration, were generated after the filing date of the '866 patent. (JTX-004-0233; Tr. 183:18-21.)

DFF149. Admitted.

Defendants Finding No. 150. The inventors of the '866 patent must have been aware of the pH dependent solubility of buprenorphine as taught by Cassidy, because otherwise they would have been unable to arrive at the lower limit of the claimed 4-6 pH range based on the data for BEMA 1 and BEMA 2 alone. (See Tr. 183:18-21.)

DFF150. Denied. Dr. Vasisht testified that he was surprised by the results he obtained with the devices he tested at pH 6 and pH 7, where the device at pH of 6 was surprisingly better than the device at pH of 7. For this reason, he tested devices with lower pH values. (Tr.753:17-756:2, 759:5-760:11.) Further, the Cassidy data is not applicable to the polymeric diffusion environment. *See* Resp. DFF57, PFF51-52.

Defendants Finding No. 151. Dr. Thisted's analyses found no statistically significant difference between BEMA 1 and BEMA 2 with respect to Cmax or AUC, meaning that any difference between the two is plausibly attributable to chance. (Tr. 946:14-947:17.)

DFF151. Denied. Dr. Thisted's analysis showed that the differences in Cmax and AUC between BEMA 1 and BEMA 2 *in isolation* are not statistically significant. (Tr.944:10-945:19); *see also* PFFs 225-237. But he testified that there were differences when one looked at the data as whole. *Id*.

PFF92. The Cmax for BEMA2-7 were 32%, 92%, 215%, 190%, 132%, and 166% higher, respectively, than the Cmax for BEMA1. (Tr.443:24-444:24, 943:8-944:9.)

PFF93. The strong trend in the Cmax data for BEMA 1-7 and the highly statistically significant differences between BEMA 3-7 compared to BEMA 1 gives a POSA confidence that the differences between BEMA 2 and BEMA 1 are not due to chance or random variation. (Tr.944:10-945:19.)

Defendants Finding No. 152. Demonstrative DDX6 (reproduced below) accurately depict how a graph of pH vs. Cmax would look with the correct pH values for BEMA 1, BEMA 2 and Suboxone®. (DDX6, *see* Tr. 948:21-24.) The white dots indicate the data provided to the PTO for BEMA 1-2, and the red lines indicate that the actual pH values were lower, and the blue dots following the red lines indicate the actual pH values provided to FDA for BEMA 1-2. The blue square is the pH value for Suboxone® that Dr. Thisted inferred, and the red square is the actual pH value for Suboxone®. The remaining blue dots are for BEMA 3-7 as reported by Dr. Finn in his declaration.

DFF152. Denied. The cited testimony does not state that the "correct" pH values for BEMA 1, BEMA 2 and Suboxone® are 6.8, 5.3, and 3.5, respectively. Dr. Thisted did not "infer" a pH value for Suboxone®. (Tr.942:5-7.) *See* Resp. DFF146, 151, PFF92-93.

Defendants Finding No. 153. During prosecution of the '843 patent, BDSI submitted the Declaration of Dr. Niraj Vasisht, signed March 23, 2017. (JTX-005-2769-776.)

DFF153. Admitted.

Defendants Finding No. 154. During prosecution of the '866 patent, BDSI argued that the Todd reference relates primarily to the stability of aqueous buprenorphine solutions and that the solutions "may merely migrate to another aqueous solution, the saliva, while the solution is in the subjects mouth." (JTX-005-2771.) However, Todd teaches sublingual delivery of

buprenorphine, and discusses the "uptake of the drug" which refers to the passage of drug through the mucosa, i.e., absorption. (DTX-0174-0003 at 2:11-17; Tr. 175:1-2.)

DFF154. Denied. Dr. Vasisht was correctly distinguishing the claimed invention from Todd, where buprenorphine is in liquid form and is held under the tongue in saliva in an aqueous environment. DTX-0174. Unlike Todd, the buprenorphine in the claimed invention is solubilized in the mucoadhesive layer in the form of a molecular dispersion and diffuses directly through the mucosa. *See* PFF23-28.

Defendants Finding No. 155. The priority date of claims 9 and 20 of the '539 patent is December 21, 2012. (JTX-0003-0001.) All prior art described above with respect to the '866 and '843 patents is also prior art to the claims of the '539 patent.

DFF155. Admitted.

Defendants Finding No. 156. International Patent Publication WO 2008/0011194 A2 ("Vasisht I") (DTX-017) published on January 24, 2008 and is prior art to the '539 patent. (D.I. 249 at 3; DTX-017-0001; Tr. 205:4-11.)

DFF156. Admitted.

Defendants Finding No. 157. Vasisht I is the publication of PCT Application PCT/US2007/016634, which is the PCT parent application to, and has the same specification as, the '866 and '843 patents. (DTX-017-0001, Tr. 292:19-25, 293:8-10; 371:4-9.)

DFF157. Admitted.

Defendants Finding No. 158. Vasisht I discloses BEMA devices and methods for the direct transmucosal administration of buprenorphine to provide enhanced uptake of buprenorphine. (D.I. 249 at 3; DTX-017 at

[0004], [0010], [0011], [0024], [0037], [0041], [0045]; Tr. 211:23-212:16; 241:13-20.)

DFF158. Admitted.

Defendants Finding No. 159. Vasisht I discloses that the use of the buprenorphine-containing devices are effective to treat "any pain known in the art, caused by any disease, disorder, condition, and/or circumstance." (DTX-017-0013-0014 at [0045]; Tr. 214:24-215:14.)

DFF159. Denied. Vasisht I actually states: "The pain can be any pain known in the art, caused by any disease, disorder, condition and/or circumstance." DTX-017, ¶ 45.

Defendants Finding No. 160. Vasisht I discloses examples of pain, including moderate to severe pain, chronic pain, or lower back pain, for which treatment with the buprenorphine-containing devices is effective. (DTX-017 at [0011], [0029], [0041], [0045]; Tr. 211:23-212:16, 212:17-24, 213:18-22, 214:24-215:25.)

DFF160. Denied. The only mention of back pain discussed in Vasisht-I is that: "breakthrough pain also occurs in patients with lower back pain." DTX-017, ¶29. "Breakthrough pain" is not chronic pain. *Id*.

Defendants Finding No. 161. Vasisht I discloses that the devices may be administered "at dosages and for periods of time effective for treatment of a subject" and in "[d]osage regimens . . . adjusted to provide the optimum therapeutic response." (DTX-017-0011 at [0036]; Tr. 212:17-24.)

DFF161. Admitted.

Defendants Finding No. 162. Vasisht I discloses that "several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation." (DTX-017-0011 at [0036]; Tr. 212:17-24.)

DFF162. Admitted.

Defendants Finding No. 163. Vasisht I discloses that a transmucosal drug delivery device containing buprenorphine may be administered at dosages and for periods of time effective for treatment of a subject. (D.I. 249 at 4; DTX-017-0011 at [0036]; Tr. 212:17-24.)

DFF163. Admitted.

Defendants Finding No. 164. Vasisht I teaches that the device containing buprenorphine provides a therapeutically effective total daily dose of buprenorphine such that pain, including chronic pain, is treated and/or alleviated. (DTX-017 at [0011], [0036], [0041], [0045]; Tr. 211:23-212:24, 213:18-22, 214:24-215:25.)

DFF164. Denied. The cited portions of Vasisht I do not describe "a therapeutically effective total daily dose of buprenorphine."

Defendants Finding No. 165. Vasisht I discloses a bioerodable mucoadhesive layer including an effective amount of buprenorphine in a polymeric diffusion environment. (DTX-017 at [0012], [0019], [0024], [0048], [0049], [0052], [0060], [0072], [0100], [0120]; Tr. 212:25-213:9.)

DFF165. Admitted.

Defendants Finding No. 166. Vasisht I discloses a BEMA device containing buprenorphine that includes a polymeric diffusion environment buffered to a pH of between about 4 and about 6, including between about 4.5 and about 5. (D.I. 249 at 3; DTX-017 at [0012], [0016], [0019], [0024], [0048], [0049], [0052], [0060], [0072], [0100], [0120], [0121]; Tr. 212:25-213:9, 240:13-19, 241:23-242:12.)

DFF166. Admitted.

Defendants Finding No. 167. Vasisht I discloses that a BEMA device including buprenorphine may include buprenorphine in an amount from about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600, or 2000 mcg.[6] (D.I. 249 at 4; DTX-017-0015-0016 at [0052]; Tr. 212:25-213:9; 373:18-374:10.) n.6: Microgram, or "mcg," is used interchangeably herein and in the prior art as "µg." One milligram ("mg") equals 1000 µg.

DFF167. Admitted.

Defendants Finding No. 168. Vasisht I further discloses that buprenorphine Cmax is dose proportional such that Cmax varies linearly with the dose administered. (DTX-017-0017-0018 at [0057]; Tr. 216:1-216:18, 325:25-326:10; 373:10-374:21.)

DFF168. Denied. Vasisht I discloses that for its transmucosal delivery devices Cmax increases in a manner proportional to dose. DTX-017, ¶57.

Defendants Finding No. 169. Vasisht I discloses a BEMA device that includes a backing layer that provides a unidirectional gradient on application to a mucosal surface, for rapid and efficient delivery of buprenorphine. (D.I. 249 at 3; DTX-017 at [0010]-[0013], [0018]-[0019], [0024], [0034], [0040], [0047], [0073], [0077], [0099]; Tr. 239:21-240:12, 242:13-243:4.)

DFF169. Admitted.

PFF94. Vasisht I does not teach any pH values for any backing or barrier layer. (Tr. 279:10-12.)

Defendants Finding No. 170. Vasisht I describes a method of preparing a buffered backing layer for the claimed devices, including a recitation of the components of the backing layer used, and the wet weight percentages of each ingredient. (DTX-017 at [0014], Example 1, [0099]; Tr. 206:3-11.) The components listed do not include an opioid antagonist.

DFF170. Denied. Defendants' reference to the "claimed device" in the proposed finding is ambiguous. Vasisht-I is not an issued patent.

Defendants Finding No. 171. Vasisht I discloses a backing layer formulation that includes the following components by weight percent converted to dry basis: sodium benzoate (0.5 wt.%), methylparaben (0.5 wt.%), propylparaben (0.1 wt.%), citric acid (0.5 wt.%), vitamin E acetate (0.05 wt.%), sodium saccharin (0.5 wt.%), hydroxypropyl cellulose (63 wt.%), hydroxyethyl cellulose (32%), titanium dioxide (2.7%), peppermint

oil (0.9 wt.%). (DTX-017-0028-0030 at Example 1, [0099]; Tr. 206:5-207:23, 209:20-210:3, 213:10-17; DDX4.31.)

DFF171. Denied. Dr. Michniak-Kohn rounded certain values for the backing layer of Example 1 of Vasisht-I, which masked the differences between the backing layer described in Vasisht-I, the backing layer for BELBUCA, and Example 1 of the '539. (Tr.283:8-15); DTX-017, Example 1; JTX-003-col.10:9-27; DTX-0019-0045. The correct calculations, as shown below, demonstrate the differences in the components of the backing layer formulation, including for propylparaben where there is a 50% difference between backing layer of Vasisht-I and BELBUCA. *See* below comparing DTX-0017, ¶99 and DTX-0019-0045.

Component	Backing layer of Vasisht I, dry formulation % weight, ***not*** rounded to one decimal point	Backing layer of BELBUCA, dry formulation % weight, ***not*** rounded to one decimal point	Percent difference
Sodium benzoate	.450	.495	**10%**
Methylparaben	.450	.449	0.2%
Propylparaben	.135	.090	**50%**
Citric Acid	.450	.495	**10%**
Vitamin E Acetate	.045	.045	(no difference)
Saccharin Sodium	.450	.495	**10%**
Hydroxypropyl Cellulose	63.063	63.154	0.1%

Hydroxyethyl Cellulose	31.532	31.543	0.03%
Titanium Dioxide	2.703	2.471	**9%**
Peppermint Oil	.901	0.764	**17.9%**

Defendants Finding No. 172. Vasisht I discloses that the subject treated may be "opioid tolerant" and/or to treat subjects "already on chronic opioid therapy." (DTX-017-0013-0014 at [0043], [0045]; Tr. 214:4-8.)

DFF172. Admitted.

Defendants Finding No. 173. Vasisht I discloses that the subject treated is "opioid-experienced," as this Court construes the term. (DTX-017-0013-0014 at [0043], [0045]; Tr. 214:4-8; D.I. 114.)

DFF173. Denied. The cited portions of Vasisht I disclose treatment of "relief for breakthrough cancer pain (BTP) in opioid tolerant patients with cancer" and breakthrough cancer pain in a subject "already on chronic opioid therapy." DTX-017, ¶¶43, 45.

Defendants Finding No. 174. Vasisht I discloses that the transmucosal drug delivery device containing buprenorphine can be administered to opioid-experienced subjects currently receiving opioid therapy. (DTX-017-0013-0014 at [0043], [0045]; Tr. 214:4-8.)

DFF174. Denied. *See* Resp. DFF173.

Defendants Finding No. 175. Vasisht I discloses that any side effects experienced by subjects treated with the devices are "mild or moderate in nature." (DTX-017-0036 at [0118]; Tr. 204:13-19, 214:9-19, 371:10-373:9, 399:16-400:8, 399:20-400:8.)

DFF175. Denied. The paragraph relied on by Defendants, paragraph 118 of DTX-0017, describes the side effects for a *fentanyl* device of Example 2 as being "mild or moderate" in nature.

Defendants Finding No. 176. Vasisht I discloses that subjects treated with the devices experience "little or no constipation." (DTX-017-0017 at [0055]; Tr. 214:8-19; 371:10-373:9; 400:9-401:12.)

DFF176. Admitted. Vashist I, however, does not describe any percentages of subjects with "little or no constipation."

Defendants Finding No. 177. U.S. Patent No. 6,231,886 ("Reder") (DTX-078) published on May 15, 2001 and is prior art to the '539 patent. (DTX-078-1; Tr. 216:19-21.)

DFF177. Admitted.

Defendants Finding No. 178. Reder is directed to buprenorphine drug delivery devices "which allow[] for reduced plasma concentrations of buprenorphine over a prolonged time period than possible according to prior art methods, while still providing effective pain management." (DTX-078-0008 at 2:63-67; Tr. 222:22-223:13, 374:22-375:11.)

DFF178. Denied. Reder teaches a *method* which allows for reduced plasma concentrations of buprenorphine over a more prolonged period than possible according to prior art methods, while still providing effective pain management. (Tr.286:19-24, 375:1-11; 429:14-20); DTX-078-0008, col.2:63-65.

PFF95. Reder teaches a POSA to maintain a relatively *flat* concentration of buprenorphine for a long period of time, which is defined by a *decrease of no more than 30% over a 48-hour* period. (Tr.431:22-433:20, 831:7-831:21); DTX-078-0010, col.6:39-45.

PFF96. Reder teaches that the preferred mode of administration to better control plasma concentrations of buprenorphine is through a *transdermal* delivery system or a *continuous intravenous infusion*, which provide a flatter continuous profile in terms of the plasma concentration. (Tr.287:4-12, 424:18-425:5, 423:19-23, 830:5-830:19); DTX-078-0009, col.3:60-65.

PFF97. A POSA would understand that Reder teaches the use of sustained release formulations to obtain the desired "flat" plasma concentrations for the extended period of time of over 12 hours. (Tr.435:13-18, 831:22-832:9.)

PFF98. In contrast, Vasisht-I describes an immediate release delivery system where buprenorphine is delivered in less than 30 minutes. The plasma buprenorphine concentration following the administration of its devices decreases more than 30-50% percent from a peak plasma buprenorphine concentration within a period of 12 hours. (Tr.833:2-834:8, 434:6-16, 435:21-436:6); DTX-017, ¶11, Fig. 3.

PFF99. A POSA would understand that immediate release drug delivery devices are not well suited for use in a method that requires a relatively constant plasma concentration which does not decrease

more than about 30 percent over a 48-hour time period. (Tr.832:10-22, 434:1-3, 435:1-7.)

PFF100. A POSA would know the teaching of Reder would not apply to an immediate delivery system, such as Vasisht-I. (Tr.435:1-18, 832:10-22.)

PFF101. Further, Reder does not teach that a buprenorphine Cmax of 0.185 ng/mL effectively treats pain as required by Claim 9 because Reder does not measure analgesia. (Tr.425:16-427:22, 831:5-6.)

> Defendants Finding No. 179. Reder discloses a mean Cmax of 184.89 pg/mL (equivalent to 0.185 ng/mL) following administration of a transdermal device including buprenorphine that was effective to treat pain in that subject. (DTX-078-0020 at Table 2; Tr. 223:14-22, 375:1-376:2.)

DFF179. Denied. Reder describes a transdermal patch that provides a mean buprenorphine Cmax of 0.185 ng/mL. DTX-078-0020, Table 2. However, Reder does not teach that a buprenorphine C_{max} of 0.185 ng/mL effectively treats pain because Reder does not measure analgesia. (Tr.425:16-427:22, 831:5-6.)

> Defendants Finding No. 180. Reder's reported mean Cmax of 0.185 ng/mL is within the claimed range of "about 0.156 ng/mL to about 0.364 ng/mL." (JTX-0003 at Claim 9; DTX-078-0020 at Table 2; Tr. 395:25-396:21.)

DFF180. Denied. Reder's Cmax teachings are inapplicable to the '539 patent claims. *See* PFF95-101.

Defendants Finding No. 181. Reder discloses, "[a]ny mode of [administration] may be utilized" to obtain the desired plasma concentrations of buprenorphine. (DTX-078 at 3:56-59; Tr. 223:23-224:4, 224:13-20.)

DFF181. A POSA reading Reder would not understand to use any mode of administration to obtain the desired plasma concentrations, or C_{max}, over a 72-hour period. *See* Resp. DFF179. Instead, Reder teaches a POSA to use a transdermal system or continuous infusion. *See* PFF91-101.

Defendants Finding No. 182. Reder discloses, "[f]or example, the buprenorphine may be administered transdermally, parenterally, sublingually, orally, buccally, rectally, etc." (DTX-078-0009 at 3:56-59; Tr. 223:23-224:4, 224:13-20.)

DFF182. Denied. See Responses to DFF181.

Defendants Finding No. 183. Bullingham I published in 1981 and is prior art to the '539 patent. (DTX-077-0001, Tr. 88:18-89:13.) The discussion of Bullingham I set forth in Section III.A.2.(b) *supra* is incorporated by reference herein.

DFF183. Admitted. Plaintiffs incorporate their responses to DFF41-45 and PFF37-45.

Defendants Finding No. 184. Bullingham I is a peer-reviewed study involving the administration of buprenorphine sublingual tablets at a total dose of 400 mcg. (DTX-077-0001-0002; Tr. 332:10-333:10.)

DFF184. Admitted.

Defendants Finding No. 185. Bullingham I describes the pharmacokinetic and pharmacodynamic results of the administration of sublingual buprenorphine tablets. (DTX-077-0001; Tr. 88:18-89:13, 332:23-333:14.) The sublingual dose was preceded by administration of 300 mcg of intravenous buprenorphine. (DTX-077-0001-0002; Tr. 332:23-333:14.) The contribution of the intravenous dose to measured concentrations of

buprenorphine in the blood was removed from the results by "stripping." (DTX-077-0002; Tr. 333:15-334:7.)

DFF185. Denied. See PFFs 37-45.

Defendants Finding No. 186. Bullingham I teaches that the Cmax resulting from administration of 400-mcg of sublingual buprenorphine was 0.74 +/- 0.16 ng/mL. (DTX-077-0003 at Table 2; Tr. 397:9-23.)

DFF186. Denied. A POSA would not view the Cmax value disclosed in Bullingham I as a reliable indicator of the expected Cmax following sublingual administration of buprenorphine tablets. See PFFs 37-45.

Defendants Finding No. 187. Bullingham II published in 1982 and is prior art to the '539 patent. (DTX-177-0001; Tr. 341:5-342:5, 397:9-23.)

DFF187. Admitted.

Defendants Finding No. 188. Bullingham II presents the results of a nearly identical, larger study of the same design as Bullingham I in 15 patients and included sublingual buprenorphine tablet doses of 400 mcg and 800 mcg. (DTX-177-0001; Tr. 341:5-342:5.) As was done in Bullingham I, the concentrations from the IV dose were subtracted from the analysis, and Bullingham II reports the concentrations from the second, sublingual dose. (Tr. 342:6-12.)

DFF188. Denied. See PFF42-42.2.

Defendants Finding No. 189. Bullingham II discloses a Cmax of 0.5 +/- 0.06 ng/mL for a 400-mcg dose of sublingual buprenorphine, and 1.04 +/- 0.27 ng/mL for a dose of 800-mcg. (DTX-177-0001, -0008 at Table 7; Tr. 397:9-23.)

DFF189. Denied. A POSA would have view the "stripped" plasma buprenorphine concentrations reported Bullingham II as reliable. See PFFs 42-42.2.

Defendants Finding No. 190. Temgesic® published on May 9, 2008 and is prior art the '539 patent. (DTX-170-0007; Tr. 401:13-402:12.) Temgesic® has been available since the early 1980s and was the sublingual buprenorphine tablet product used in the studies of Bullingham I and Bullingham II. (Tr. 397:9-17, 401:16-23.)

DFF190. Denied. The cited testimony states that DTX-170 purports to be "the Australian package insert" of Temgesic®, and there is nothing in the document stating that it was published on May 9, 2008. Bullingham-I does not state that the studies described therein used Temgesic. DTX-0170.

Defendants Finding No. 191. Temgesic® describes sublingual tablets containing 216-mcg buprenorphine. (DTX-170-0001.)

DFF191. Admitted.

Defendants Finding No. 192. Temgesic® is a "[s]trong analgesic" indicated for the treatment of pain. (DTX-170-0003.)

DFF192. Denied. Temgesic® is not indicated for the treatment of chronic pain but rather is indicated for the "short term (not more than one week) relief of . . . pain." DTX-170-0003.

Defendants Finding No. 193. Temgesic® discloses that "less than 1% of patients" treated with Temgesic® experienced constipation as an "[a]dverse reaction[]." (DTX-170-0005; Tr. 401:13-402:12.)

DFF193. Denied. There is nothing in the label that shows this information only pertains to the sublingual tablets. The label also includes information about the injectable formulation which bypasses first pass metabolism. DTX-170-0001.

Defendants Finding No. 194. Vasisht I discloses a method of treating moderate to severe chronic low back pain (as required by claim 9), and a method of treating chronic pain (as required by claim 20). (JTX-0003-0015-0016 at Claims 9, 1; DTX-017 at [0004], [0010], [0011], [0024], [0029], [0037], [0041], [0045]; Tr. 211:23-212:24, 213:18-22, 214:24-215:25, 241:13-20.)

DFF194. Denied. *See* Resp. DFF160.

Defendants Finding No. 195. Vasisht I teaches the "once or twice daily" administration of "a mucoadhesive bioerodable drug delivery device to the oral mucosal surface of the subject" "in need thereof." (JTX-0003-0015-0016 at Claims 9, 1; DTX-017 at [0010], [0036]; Tr. 212:17-24.)

DFF195. Denied. The cited portions of Vasisht-I do not disclose "once or twice daily" administration." DTX-017-0036.

Defendants Finding No. 196. Vasisht I teaches a device comprising "a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a buffered polymeric diffusion environment, wherein the polymeric diffusion environment is a buffered environment having a pH of between about 4 and about 6." (JTX-0003 at Claims 9, 20; DTX-017 at [0024], [0052], [0072], [0019], [0048], [0049], [0012], [0060], [0064], [0100], [0120]; Tr. 212:25-213:9.) Vasisht I teaches that the amount of buprenorphine included in the bioerodable mucoadhesive layer may be between "about 100 [mcg] and about 0.9 mg." (JTX-0003-0015 at Claim 1; DTX-017-0017-0018 at [0057]; Tr. 216:1-17, 373:10-374:21.)

DFF196. Denied. The cited portion of Vasisht I does not state that "the amount of buprenorphine included in the bioerodable mucoadhesive layer may be between 'about 100 mcg and about 0.9 mg.'"

Defendants Finding No. 197. Vasisht I teaches administration of a "total daily dose of buprenorphine" that "is effective for treating moderate to severe chronic low back pain." (JTX-0003-0015-0016 at Claim 9; DTX-017 at [0036], [0011], [0041], [0045]; Tr. 211:23-212:24, 213:18-22, 214:24-215:25.)

DFF197. Denied. *See* Resp. DFF160.

Defendants Finding No. 198. Vasisht I teaches a method "wherein the subject is an opioid-experienced subject." (JTX-0003-0015-0016 at Claim 9, Claim 20; DTX-017 at [0043], [0045]; Tr. 214:4-18; D.I. 114.)

DFF198. Denied. *See* Resp. DFF173.

Defendants Finding No. 199. Vasisht I teaches a method "wherein the subject treated experiences mild or moderate common opioid adverse effects, or no common opioid adverse effects." (JTX-0003-0015-0016 at Claim 9, Claim 20; DTX-017 at [0055], [0118]; Tr. 204:13-19, 214:9-19, 371:10-373:9, 399:20-400:8.)

DFF199. Denied. *See* DFF175.

Defendants Finding No. 200. Claims 9 and 20 further require that the backing layer is buffered to a pH between about 4.0 and about 4.8 and does not include an opioid antagonist. JTX-003-0015-0016 at Claim 9, Claim 20. Vasisht I discloses a method of preparing a backing layer for the claimed devices, including a recitation of the components of the backing layer used, and the wet weight percentages of each ingredient. (DTX-017 at [0014], Example 1, [0099]; Tr. 206:3-207:23, 209:20-210:3, 213:10-17; DDX4.31.)

DFF200. Denied. Vasisht-I describes an example of a backing layer formulation but not "for the claimed devices," and this phrase is vague in the context of this finding.

Defendants Finding No. 201. Example 1 of the '539 patent recites a method of preparing a backing layer for the devices to be used in the claimed method, including a recitation of the components of the backing layer used, and a dry weight percentage of each ingredient. (JTX-003-0012 at Example 1, 10:9-27; Tr. 206:12-207:23.) The listed ingredients for the backing layer formulations in Vasisht I and Example 1 of the '539 patent are the same. (JTX-003-0012 at Example 1, 10:9-27; DTX-017-0028-0030 at Example 1, [0099]; Tr. 206:3-207:23; DDX4.31.)

DFF201. Denied. *See* PFF171.

Defendants Finding No. 202. The weight percentages of the ingredients in the example backing layer of Vasisht I and the backing layer disclosed in the '539 patent are materially identical for most components. (Tr. 206:12-207:23; DDX4.31.) While the two formulations slightly differ with respect to the proportions of peppermint oil and titanium dioxide, a POSA would have known that peppermint oil (flavoring agent) and titanium dioxide (coloring agent), as ingredients in the backing layer formulation, would not affect the pH of the layer. (*See* DTX-019-0023; Tr. 207:6-16; DDX4.31.)

DFF202. Denied. *See* PFF171.

Defendants Finding No. 203. A POSA would have known that the pH of the backing layer disclosed in Vasisht I would have inherently been the same as that disclosed in Example 1 of the '539 patent. (Tr. 206:12-207:23 at 207:17-23.)

DFF203. Denied. *See* PFF171.

Defendants Finding No. 204. BELBUCA includes a backing layer having a pH of 4.5. (Tr. 207:17-23, 574:13-576:25 at 574:13-21, 575:24-576:8, 576:16-576:25.) This pH data was obtained from the same backing layer formulation as that reported to the FDA as part of the BELBUCA NDA. (Tr. 573:10-574:5.)

DFF204. Denied. The pH of the backing layer of BELBUCA "stayed within the range of 4.5 to 4.7." (Tr.576:13-25.)

Defendants Finding No. 205. According to BDSI's internal documents, the backing layer composition for the commercial formulations of BELBUCA, referred to as F14 and F24, are identical in components and proportions to the backing layer disclosed in the '539 patent. (JTX-003-0012 at Example 1; *see* DTX-019-0041, -0044, and -0045 (Table 21) (describing the backing layer for the final formulations of BELBUCA, F14 and F24); Tr. 206:12-209:17; DDX4.31.)

DFF205. Denied. The numbers for the components and proportions of the backing layer in the specification of the '539 patent JTX-0003, col.10:9-27 are

not identical to the numbers for the components and proportions of the backing layer for BELBUCA, as described in DTX-019-0045, Table 21.

Defendants Finding No. 206. The backing layer composition for the commercial formulations of BELBUCA are therefore materially identical to the backing layer composition disclosed in Vasisht I. (DTX-017 at Example 1; DTX-019-0045 at Table 21; Tr. 206:12-209:17.)

DFF206. Denied. *See* PFF171.

Defendants Finding No. 207. A POSA would have known that the backing layer disclosed by Vasisht I has the same pH (4.5) as does the backing layer described in the '539 patent and included in BELBUCA. (Tr. 207:17-23, 209:10-210:3.) A pH of 4.5 is within the claimed range of "about 4.0 to about 4.8." (Tr. 209:10-210:3.)

DFF207. Denied. *See* PFF171.

Defendants Finding No. 208. During prosecution of the '539 patent, the PTO repeatedly rejected the claims over Vasisht I. (JTX-0006-0075-0081, JTX-0006-0157-0167, JTX-0006-0193-0204, JTX-0006-0233-0256, JTX-0006-3790-3806, JTX-0006-4043-4063, JTX-0006-4116-4132.) Following one such rejection, Dr. Vasisht submitted a declaration stating, "we did recently remake the backer formulation" described in Vasisht I, and purportedly measured the pH of that formulation to be, on average, 5.61. (JTX-0006-4100-4102 at JTX-006-4101; Tr. 210:8-211:6.) The measurements Dr. Vasisht reported cannot have been accurate in view of the similarities between the backing layer formulation of Vasisht I and that of the '539 patent and BELBUCA. (JTX-0006-4101, Tr. 210:4-211:22.)

DFF208. Denied. *See* PFF171.

Defendants Finding No. 209. A POSA would have been motivated to incorporate the backing layer described by Vasisht I into a device including buprenorphine in the mucoadhesive layer instead of fentanyl, which is recited in Vasisht I. (DTX-017-0029 at [0099].) Vasisht I recites an example of such a preparation, stating that "[d]evices containing buprenorphine were also produced using the same method as described in Example 1, except that buprenorphine was added to the mucoadhesive polymeric diffusion environment instead of fentanyl citrate." (DTX-017-0037 at Example 3,

[0120].) Vasisht I thus provides explicit teaching that buprenorphine and fentanyl are interchangeable for treating pain in the methods described.

DFF209. Denied. Dr. Vasisht (an inventor) testified that buprenorphine and Fentanyl do not behave the same way in the devices described in Vasisht-I. (Tr.754:21-756:2.) Fentanyl was a known Schedule-II drug, and buprenorphine was a known schedule III drug. Further, the cited portions of Vasisht-I do not provide "explicit teaching that buprenorphine and fentanyl are interchangeable for treating pain in the methods described."

Defendants Finding No. 210. Claim 20 requires that "between about 1.5%-8.5% of subjects treated experience constipation as a [treatment emergent adverse event] TEAE". (JTX-0003 at Claim 20; Tr. 400:9-17.) This limitation was added during prosecution (*see* JTX-0006-0217), but was never relied-upon in any subsequent argument by the applicants as patentable independent of claim 1. (JTX-0006-2319-2322; JTX-0006-3836-3844; JTX-0006-4091-4099; JTX-0006-4141-4149).

DFF210. Admitted.

Defendants Finding No. 211. The prior art Vasisht I and Temgesic® teach that low incidences of constipation were known to be associated with transmucosal administration of buprenorphine. (DTX-017-0017 at [0055] (treatment the device of the present invention causes "little or no constipation"); Tr. 214:8-19, 371:10-373:9, 400:9-401:2 at 400:18-23; DTX-170-0005 (transmucosal, sublingual administration of buprenorphine results in "less than 1%" of subjects experiencing constipation); Tr. 401:13-402:12.)

DFF211. Denied. *See* Resp. DFF190, 192-93, 176.

Defendants Finding No. 212. A POSA would further have expected that 5-10 percent of patients on chronic opioid therapy experience constipation as a side effect, which overlaps with the claimed range. (Tr. 401:3-13.) A POSA would also have understood that side effects like constipation are the result of buprenorphine and the dosage amount, and not the drug delivery system. (Tr. 501:25-503:13 at 503:6-13.)

DFF212. Denied. Dr. Shafer is an anesthesiologist and is not an expert in pain management. (Tr.446:24-447:12.) Further "the old MU agonists have had a minimum 40 percent and, again, some surveys up to 80 percent incidence of constipation." (Tr.881:13-17.) Further, due to the devices of the claimed invention, less buprenorphine can be used which results in less side effects.

Defendants Finding No. 213. Asserted claim 20 also requires that the device provides, "a steady-state Cmax of plasma buprenorphine in a range between about 0.156 and about 0.364 ng/mL."[7] (JTX-0003-0015 at Claim 1; Tr. 213:23-214:3, 373:10-17.) n.7: A "nanogram" or "ng" is one billionth of a gram and a "milliliter" ("mL") is one thousandth of a liter.

DFF213. Admitted.

Defendants Finding No. 214. Cmax is a pharmacokinetic parameter that refers to "the maximum plasma concentration of a drug following administration." (Tr. 325:7-11.) "Cmax depends on the drug, on the device, and on the dose." (Tr. 325:16-19.) Steady-state Cmax refers to the Cmax observed when repeated doses of the drug are administered, and thus further "depends on the dosing interval." (Tr. 326:22-327:11.) Steady-state Cmax is a pharmacokinetic parameter that depends on a given dose, in a given device, over a given dosing interval. (Tr. 326:22-327:11.)

DFF214. Denied. The trial testimony does not substantiate this finding.

Defendants Finding No. 215. A POSA would have been motivated to use the method and device taught by Vasisht I to achieve a steady-state Cmax in the claimed range as taught by Reder with a reasonable expectation of success. (Tr. 224:13-20, 375:12-376:2, 395:25-397:8 at 396:14-17.) Vasisht I discloses buprenorphine, the claimed BEMA device, the claimed dosage range, the dosing interval, and the dose proportionality of buprenorphine. Section IV.A.1 *supra*. Reder teaches a buprenorphine Cmax of 0.185 ng/mL, squarely within the claimed range, that is associated with effective pain management. (DTX-078-0020 at Table 2; Tr. 223:14-22, 375:12-376:10, 395:25-397:8.) A POSA in view of Reder would have understood that a concentration 0.185 ng/mL would provide effective pain relief. (Tr. 375:21-

376:2, 396:18-21.) A POSA would have understood, in view of Reder's disclosure that the transdermal device releases buprenorphine over several days, that the Cmax of 0.185 ng/mL in Table 2 would be a steady-state value. (DTX-078-0019-0020 at Example 1 (24:46-49, 26:10-19); Tr. 375:12-376:2, 395:25-397:8.)

DFF215. Denied. PFF95-101.

Defendants Finding No. 216. Vasisht I discloses a wide range of buprenorphine doses spanning about two orders of magnitude from 25 mcg to 2000 mcg. (DTX-017 at [0052], Tr. 374:2-10). Some of these doses are too high to achieve a Cmax within the claimed two-fold range of Cmax values. (Tr. 373:18-374:22.)

DFF216. Denied. The trial testimony does not substantiate the proposed assertion.

Defendants Finding No. 217. A POSA would understand Vasisht I's drug delivery device could be configured to provide the steady-state Cmax taught by Reder in order to effectively treat chronic pain. (Tr. 395:25-397:1.)

DFF217. Denied. PFF95-101.

Defendants Finding No. 218. A POSA would have understood that both Vasisht I and Reder taught that buprenorphine may be effectively administered to treat or manage pain. (DTX-017-0013-0014 at [0045]; Tr. 214:24-215:14; DTX-078-0008 at 2:63-67; Tr. 222:22-223:13, 374:22-375:11.)

DFF218. Denied. Reder and Vasisht-I teach different methods. Vasisht teaches an immediate release system, and Reder teaches an extended-release system. *See* PFF95-101.

Defendants Finding No. 219. A POSA would have understood that the critical disclosure in Reder is a buprenorphine Cmax within the claimed range that is effective to treat pain, not the particular route of administration. (Tr. 375:21-376:10, 377:23-378:20.)

DFF219. Denied. *See* PFF95-101. Dr. Shafer admits a POSA would understand that for buprenorphine, C_{max} and the relation of C_{max} to dose differ between mucoadhesive delivery devices and transdermal delivery systems. Tr.424:4-11.

Defendants Finding No. 220. A POSA further would have understood that Reder's disclosure is not restricted to transdermal delivery devices, and provides guidance relevant to transmucosal devices, for example, as taught by Vasisht I. (DTX-078-0009 at 3:56-59, Tr. 223:23-224:6; 224:13-20.) Reder explicitly discloses that "[a]ny mode of [administration] may be utilized," including "buccal[]" administration. (DTX-078-0009 at 3:56-59, Tr. 223:23-224:6; 224:13-20.)

DFF220. Denied. *See* PFF95-101.

Defendants Finding No. 221. A POSA would have understood that the delivery mechanism itself is not relevant to whether the resulting blood concentrations are associated with effective pain relief. (Tr. 376:3-10, 376:25-377:2, 377:8-15, 377:22-379:8.)

DFF221. Denied. See PFF95-101.

Defendants Finding No. 222. A POSA further would have understood that Reder's disclosure is not restricted to transdermal devices, and provides guidance relevant to transmucosal devices, for example, as taught by Vasisht I. Reder explicitly discloses that "[a]ny mode of [administration] may be utilized," including "buccal[]" administration. (DTX-078-0009 at 3:56-59; Tr. 223:23-224:6; 224:13-20.)

DFF222. Denied. See PFF95-101.

Defendants Finding No. 223. A POSA would have been motivated, with a reasonable expectation of success, to select doses of buprenorphine, as taught by Vasisht I, for use in the device of Vasisht I to provide a Cmax within the claimed range, as taught by Reder. (DTX-017 at [0052], [0057]; DTX-078-0020 at Table 2; Tr. 373:10-375:2, 395:25-397:1.)

DFF223. Denied. *See* PFF95-101.

Defendants Finding No. 224. As discussed above, Bullingham I and Bullingham II recite the Cmax resulting from transmucosal administration of buprenorphine at 400-mcg and 800-mcg dosages. (DTX-077-001; DTX-177-001; Tr. 397:9-23.) Although the Cmax values disclosed in Bullingham I and Bullingham II are higher than those in the claimed range, a POSA would have used those values to calculate a mean buprenorphine Cmax/mcg of 0.0015 ng/mL. (Tr. 397:18-396:9, DDX3.66.)

DFF224. Denied. A POSA would not view the C_{max} values disclosed in Bullingham I and Bullingham II for sublingual administration as reliable. *See* PFF37-45. A POSA would not have been motivated or reasonably expected to successfully achieve a steady state Cmax in the range between about 0.156 ng/mL and 0.364 ng/mL. Tr.834:17-836:15. A POSA would have understood that the Cmax levels disclosed in Bullingham I and Bullingham II are above the claimed steady-state Cmax range.

PFF102. Bullingham II, Table 7, shows an average Cmax for the 400 mcg dose of approximately 0.5 ng/mL and an average Cmax for the 800 mcg dose of approximately 1 ng/mL, and a POSA would have expected that at steady state, the Cmax levels would increase. Tr.835:14-836:6; DTX 177-0008.

Defendants Finding No. 225. A POSA would have selected a dose from those recited in Vasisht I that would produce the desired Cmax, i.e., within the claimed range. (Tr. 397:24-399:14.) For example, using the per-microgram Cmax calculated above, a dose of 200-mcg, as recited in Vasisht I, would produce a Cmax of about 0.29 ng/mL. (Tr. 398:10-399:9.)

DFF225. Denied. *See* Resp. DFFs 224; PFF102.

Defendants Finding No. 226. A POSA would have understood that a Cmax calculated based on Bullingham's values would not have been consequentially different from a steady-state Cmax. (Tr. 399:6-15)

DFF226. Denied. *See* Resp. DFF224; PFF95-102.

Defendants Finding No. 227. BDSI's expert Dr. Taft testified, "changing" or "lower[ing]" the pH of the backing layer resulted in an increase of bioavailability, but he nowhere testified what the pH for the backing layer should be changed (or lowered) to be in order to obtain such an increase. (Tr. 804:2-806:19 at 804:9-804:13, 805:14-18.)

DFF227. Denied. *See* PFF103-104.

Defendants Finding No. 228. BDSI has not provided any evidence that any improved bioavailability is provided by backing layers having a pH encompassed by the claims. BDSI relies on data from confidential, non-public BDSI and Endo documents that discuss the testing of different backing layer formulations (identified as "F1," "F2," "M1," and "M2") that either included or did not include citric acid. (Tr. 804:17-805:7; 805:22-806:2). No pH information is provided for any of these tested formulations.

DFF228. Denied. *See* PFF103.

PFF103. Dr. Taft offered testimony about the pH range of the backing layer as claimed by the '539 patent, between about 4.0 and about 4.8. Tr.804:2-13.

PFF104. Dr. Taft testified that the pH of the backing layer affected the uptake of buprenorphine, and that a POSA would not have expected such results. Tr.804:10-806:19.

Defendants Finding No. 229. The prior art, particularly Vasisht I, discloses the use of citric acid in the backing layer of the device. (DTX-017-0029 at [0099]; Tr. 844:13-845:22.) As discussed above in Section IV.B *supra*, Vasisht I also discloses that the backing layer has substantially the

same composition as the example provided by the '539 patent, and has a pH of 4.5, within the claimed range. (Tr. 206:3-210:3.)

DFF229. Denied. *See* Resp. DFF171.

Defendants Finding No. 230. BDSI provides no comparison of the components or properties of the device described in the '539 patent relative to the device described in Vasisht I.

DFF230. Denied. *See* Resp. DFF71.

Defendants Finding No. 231. Any purported unexpected properties provided by the backing layer encompassed by claims 9 and 20 of the '539 patent would have also been provided by the backing layer disclosed in Vasisht I. (*See* Tr. 139:15-141:5 (defining and discussing bioavailability); 206:3-210:3.)

DFF231. Denied. *See* Resp. DFF171. As Dr. Michniak-Kohn testified, "if formulations of the compared samples are not the same other than pH, a [POSA] cannot draw any conclusion about the impact of pH, in particular, on the resulting properties of the samples, like Cmax and bioavailability. Tr.253:22-254:16.

Defendants Finding No. 232. U.S. Patent Publication US2009/0264385 ("Crowley"), published on October 22, 2009, discloses the use of citric acid to lower the pH of the backing layer of a drug delivery device, and further discloses that modifying the pH of the backing layer can be used to control the behavior of the device. (DTX-179 at [0002], [0134]; Tr. 224:21-226:9.)

DFF232. Denied. Crowley teaches modifying the pH of the backing layer to "reduce or eliminate that chemical degradation," and is not relevant to the issues here, which concern enhanced uptake. Tr.662:21-664:1, 285:6-11, 284:24-285:5.

Defendants Finding No. 233. U.S. Patent Publication US2004/0180080 ("Furusawa") teaches that the pH of the layers of a disintegrating drug

delivery device influence the characteristics of the layers and overall device. (DTX-187-0015 at [0099]; Tr. 226:10-227:8.)

DFF233. Denied. The cited paragraph in Furusawa discuss the characteristics of the pH-adjusting agent, not the layers and overall devices. DTX-187-0015, ¶99.

Defendants Finding No. 234. A POSA would have expected, in view of the general prior art, that modification of the pH of the backing layer in the claimed drug delivery device, for example, by inclusion of citric acid, would be expected to alter the device's behavior. (Tr. 226:19-228:7, 228:8-229:6.)

DFF234. Denied. The issue is enhanced uptake, not the generalized behavior of the device. See Resp. DFF 232.

Defendants Finding No. 235. The asserted claims do not mention addiction, abuse or misuse (Tr. 499:15-17); risk of respiratory depression or buprenorphine's ceiling effect (Tr. 501:21-24); the risk of prolongation of the QT interval (Tr. 506:5-7); and make no mention of either DEA scheduling or ease of prescribing (Tr. 490:20-491:1.)

DFF235. Admit that those specific features are not specifically recited in the claim but deny that they are required to be incorporated into the claim as BELBUCA embodies the asserted claims (D.I. 245, 2), and does has a low risk of addiction, abuse, and misuse, low risk of respiratory depression, low risk of QT prolongation, and is a schedule III drug. See PFF105-114.

PFF105. BELBUCA has a low risk of addiction, abuse, and misuse; low risk of respiratory depression; low risk of QT prolongation; effectively treats chronic pain, and is a schedule III drug. The sales of BELBUCA have continued to rise in a market where sales of other

opioids have fallen. (Tr.922:5-9, 922:20-25, 540:11-15, 874:24-875:12, 880:24-881:12, 884:24-886:13, 887:16-890:23, 896:22-898:7.)

PFF106. As a Schedule III medicine, the DEA has determined that BELBUCA is less prone to abuse than the schedule II opioids like fentanyl and oxycontin. (Tr.539:4-18, 491:20-492:8, 765:15-24, 871:9-15.)

PFF107. Opioid-induced constipation is a serious debilitating problem for patients, and there is a whole class of medicines that have been developed to treat this disorder. (Tr.873:12-874:13.)

PFF108. For BELBUCA, the rate of constipation among both opioid-naïve and opioid-experienced patients administered is low and "similar to placebo." JTX-433-0010; JTX-404-0008, 0008; JTX-405-0005.

PFF109. For other opioids, constipation AEs has been reported as experienced by up to 70% of patients, and an active bowel regiment is typically required to reduce constipation, including the administration of prescription drugs. (Tr. 873:12-874:13.)

PFF110. There has been no evidence that BELBUCA caused respiratory depression in any of its clinical trials. (JTX-404-0007;

JTX-433-0010; JTX-405-0007.) "Respiratory depression was not induced following the administration of BELBUCA to over 2400 unique subjects." (Tr.886:3-5; PTX-1060; PTX-1059.) There were "just two adverse events of respiratory failure and neither of them were considered related to buprenorphine." (Tr.886:6-8.)

PFF111. And as a Schedule III drug, doctors are more easily able to prescribe and refile prescriptions for BELBUCA without the limitations that are required with Schedule II drugs. (Tr.492:9-10, 874:24-875:12, 766:3-8, 870:23-872:8.)

PFF112. Butrans® has problems with irritation at the site of application, and BELBUCA does not. (Tr. 765:25-766:2, 894:21-895:5; JTX-0417-0001, 0009-0010.)

PFF113. Butrans® was approved only in low doses (maximum of 20 micrograms per hour) that for many patients is a "limited dose and ineffective dose" for many chronic pain patients. (Tr.551:25-552:17, 915:24-916:11; JTX-417-0001; JTX-0460-0002.) There was a concern that Butrans® in doses above 40 micrograms caused an elevated risk of QT prolongation. (Tr.896:22-897:12.) Accordingly, as of the '539 patent's 2012 filing date, Butrans® carried a black box

warning about QT risk. (*Id.*; Tr.552:18-25, 554:18-23; JTX-0417-0001.)

PFF114. BELBUCA never had a black box warning with respect to QT prolongation. (JTX-233; Tr. 910:17-911:6.)

> Defendants Finding No. 236. With respect to addiction, abuse or misuse, there is no difference between administration by transdermal or buccal routes. (Tr. 497:18-21.) With respect to respiratory depression and buprenorphine's ceiling effect, the effects of buprenorphine are the same irrespective of how it is administered, including between Butrans® (transdermal) and BELBUCA (buccal). (Tr. 501:12-15.) The risk associated with QT prolongation is a function of buprenorphine, not the route of administration. (Tr. 506:2-4.) The risk of adverse events for BELBUCA is similar to the risk associated with Butrans®, are typical for an opioid, and are the result of the properties of the buprenorphine itself. (Tr. 501:25-503:13.)

DFF236. Denied. Butrans® was not available as of the 2006 filing date of the '866 patent and '843 patents. In terms of the '539 patent, because of the bioavailability of the product, Belbuca delivers higher doses of the medicine than Butrans, but in a safe and effective way, as opposed to other opioids. *See* PFF105-114. Further, the differences between Reder (disclosing a transdermal formulation like Butrans®) and Vasisht I described above demonstrate that Defendants' assertion is false. Resp. DFF178; PFF95-PFF101; Tr.428:18-429:11, 829:11-22; DTX-078-0008, col.2:8-16.

> Defendants Finding No. 237. Drugs can be reclassified by DEA due to changing circumstances; for example, hydrocodone was a Schedule III for decades, but was recently re-classified as a schedule II. (Tr. 488:9-18.)

DFF237. Admitted.

Defendants Finding No. 238. Buprenorphine was classified as a schedule II opioid in 1981 and was re-classified as a schedule III opioid in 2002. (JTX-471-0003; Tr. 480:10-17.)

DFF238. Admitted.

Defendants Finding No. 239. As of the early to mid-2000s, Dr. Fine testified that he and others of the field began becoming concerned regarding the number of opioid related fatal poisonings, and became aware that the prescription opioids were starting to fall into the category of substance abuse, misuse and diversion. (Tr. 548:13-549:12.)

DFF239. Denied. Both Dr. Rauck and Dr. Fine testified that opioid abuse, misuse, and addiction disorder was a problem in the *early* 2000's, and, in any event, prior to 2006. (Tr.548:16-549:8, 864:21-865:21, 935:10-936:22.)

Defendants Finding No. 240. The earliest documentary evidence in the record that points to the opioid crisis was a NCHS Data Brief that was published in September 2009. (JTX-410-0002; Tr. 930:19-932:8.) The Data Brief highlights trends in fatal opioid analgesic-related poisonings from the years 1999-2006. (JTX-410-0001.)

DFF240. Denied. JTX-399 was submitted in 2008, and talks about the opioid abuse problem as a "serious health problem," citing a 2005 document that relied on 2004 data. Further, the NCHS Data Brief also points to articles published prior to 2006 to support its assertions. JTX-399-0002, 0012 n.9; Tr.543:10-544:2, 546:1-547:19, 931:5-932:5; JTX-410-0007.

Defendants Finding No. 241. Dr. Rauck testified that although BELBUCA has been on the market since 2016, the opioid crisis continues, and BELBUCA did not solve the opioid crisis. (Tr. 904:5-905:1.) Dr. Rauck concedes that despite the introduction of BELBUCA, there is still a need for chronic pain treatment with a lesser potential of addiction, abuse and misuse,

stating, "there continues to be an unmet need, absolutely." (Tr. 910:4-9.) Dr. Rauck's implies that the need may be met by "some really exciting, novel, non-opioid analgesics that would hopefully get away from all of this." (Tr. 910:4-9.)

DFF241. Denied. Trial testimony does not substantiate Defendants' proposed "implication." Dr. Rauck testified that BELBUCA met an unmet need for chronic pain patients and provided an alternative to the prescription drugs that led to the opioid crisis. (Tr.897:13-898:7, 904:19-23.) The unmet need in question is not to solve the opioid crisis, but to provide a safer treatment for chronic pain patients, as Dr. Rauck testified to. *See* PFF105-114.

Defendants Finding No. 242. The BELBUCA product label contains a "Black Box Warning," which is the highest level of warning required by FDA on drug labels. (JTX-233-0001; Tr. 495:14-20, 496:9-13.)

DFF242. Admit that the label contains a black box warning but deny that is warning is reflective of BELBUCA's performance in its clinical trials, as opposed to a general warning that applies to the class of opioids required by the FDA. Tr.909:18-21. For example, BELBUCA has only a small percentage of QT prolongation. Tr.896:24-897:12.

Defendants Finding No. 243. The BELBUCA label states: "BELBUCA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess a patient's risk before prescribing and monitor regularly for these behaviors and conditions." (JTX-233-0001; Tr. 496:25-497:17, 498:11-499:10.)

DFF243. Admit that the label contains the cited language but deny that is reflective of BELBUCA's performance in its clinical trials, as opposed to a general warning that applies to the class of opioids required by the FDA. Tr.909:18-21.

Defendants Finding No. 244. The BELBUCA label states, "Misuse or abuse of BELBUCA by chewing, swallowing, snorting or injecting buprenorphine extracted from the buccal film will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death." (JTX-233-3.)

DFF244. *See* Resp. DFF 243.

Defendants Finding No. 245. The BELBUCA label states "Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of BELBUCA to reduce risk." (JTX-233-0001; Tr. 499:18-500:19.)

DFF245. *See* Resp. DFF 243.

Defendants Finding No. 246. The BELBUCA label states, under "Warnings and Precautions": "Risk of Prolonged QTc Interval: Avoid in patients with Long QT syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications." (JTX-233-0001; Tr. 504:24-506:1, 910:25-911:6.)

DFF246. *See* Resp. DFF 242, PFF105-114.

Defendants Finding No. 247. The BELBUCA label states: "Do not exceed a dose of BELBUCA 900 mcg every 12 hours due to the potential for QTc interval prolongation." (JTX-233-0005; Tr. 915:2-915:16, 916:12-16.)

DFF247. *See* Resp. DFF 243, PFF 79.

Defendants Finding No. 248. The BELBUCA label states under "Adverse Reactions "Most common adverse reactions (>5%) include: nausea, constipation, headache, vomiting, dizziness, and somnolence." (JTX-233-0001; Tr. 501:25-502:21.)

DFF248. Admitted.

Defendants Finding No. 249. The Butrans® label also contains a "Black Box Warning." (DTX-115-0001, Tr. 497:19-498:2.)

DFF249. Denied. DTX-115, the label referred to in this finding, is dated June 2014, and thus, is not prior art to any of the patents-in-suit and is not relevant. (DTX-115-0001.)

Defendants Finding No. 250. The Butrans® label states: "BUTRANS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess a patient's risk before prescribing and monitor regularly for these behaviors and conditions." (DTX-115-0001; Tr. 498:11-499:10.)

DFF250. Denied. *See* Resp. DFF249.

Defendants Finding No. 251. The Butrans® label states: "Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of Butrans to reduce risk." (DTX-115-0001; Tr. 497:22-498:19.)

DFF251. Denied. *See* Resp. DFF249.

Defendants Finding No. 252. The Butrans® label states, under "Warnings and Precautions": "Avoid in patients with Long QT syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications." (DTX-115-0001; Tr. 504:24-506:1, 910:25-911:6.)

DFF252. Denied. *See* Resp. DFF249.

Defendants Finding No. 253. The Butrans® label states under "Adverse Reactions "Most common adverse reactions (>5%) include: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash." (DTX-115-0001; see also JTX-417-0001; Tr. 502:22-503:13.)

DFF253. Denied. *See* Resp. DFF249.

Defendants Finding No. 254. Mr. Guy Donatiello testified as the corporate representative of Endo Pharmaceuticals, regarding the relationship between Endo Pharmaceuticals and BDSI with respect to the patents-in-suit and BELBUCA, contracts, licenses or other agreements concerning the patents-in-suit and BELBUCA, any assessments regarding the commercial or medical need for BELBUCA, and the basis for Endo's decision to discontinue development and/or commercialization of BELBUCA. (Tr. 464:6-10; DTX-038-0050-0052.)

DFF254. Admitted.

Defendants Finding No. 255. Effective January 25, 2012, Endo entered into a license and development agreement with BDSI regarding BELBUCA in which Endo obtained a license to develop, use, commercialize, distribute and sell BELBUCA. (Tr. 465:24-466:10; JTX-357-0002; see Tr. 475:10-19) Under the terms of the agreement, Endo agreed to pay BDSI an upfront payment of 30 million dollars, tens of millions of dollars in the form of milestone payments, as well as product royalties. (JTX-0357-0030-33; see Tr. 475:10-19.)

DFF255. Denied. Endo and BDSI entered a license agreement on January 5, 2012. JTX-357-0001; Tr.466:6-10. Endo agreed to pay BDSI up to 180 million dollars. JTX-357-0030-0032.

Defendants Finding No. 256. Endo sought priority review from FDA in connection with the NDA for BELBUCA, contending that the drug satisfied and unmet medical need. The request was denied because there was already a Schedule III buprenorphine product available (Butrans®) and Endo had failed to provide evidence that BELBUCA would represent a significant improvement over existing therapies. (Tr. 507:12-509:4; DTX-112-0004.)

DFF256. Denied. The FDA and Dr. Fine addressed only Butrans®, not multiple therapies. (DTX-112-0004; Tr.509:5-6.) Further, at that time, there was much more limited data available for BELBUCA.

Defendants Finding No. 257. Following launch, sales of BELBUCA lagged behind Endo's goal. (Tr. 467:11-19; DTX-043-0003.) According to Endo internal meeting minutes, as of June 2016, the unmet need that BELBUCA was trying own was not defined in the marketplace. Endo's corporate representative interpreted this statement as indicating, "people aren't aware of the unmet need that BELBUCA is trying to address." (Tr. 467:20-468:14; DTX-044-0002.)

DFF257. Denied. Mr. Cornwall, who was responsible for marketing BELBUCA while at Endo, testified that for BELBUCA, sales were in line with what he expected based on where the pain marketplace was at the time. Tr.765:8-14. Endo's corporate representative also testified that the sales of Belbuca were not the reason Endo returned Belbuca to BDSI. Tr.473:8-14.

Defendants Finding No. 258. By December 2016, Endo had made the decision to return BELBUCA to BDSI. (Tr. 468:15-470:3; JTX-0358-0001.) Endo's corporate representative testified that the reason for returning BELBUCA to BDSI was that Endo intended to get out of the business of promoting branded opioids. (Tr. 470:4-471:1.)

DFF258. Denied. Endo's corporate witness testified that the only factor he was aware of that influenced Endo's decision to return BELBUCA to BDSI was "the cessation of *promoting* branded opioids." Tr.471:5-21; JTX-358.

Defendants Finding No. 259. Endo continued to sell its oxymorphone opioid product Opana® until summer of 2018, at which time it withdrew the product from the market due to FDA pressure. (Tr. 560:7-22). Endo still sells the opioid analgesic Percocet, which is currently listed on its website. (Tr. 492:11-25, 555:16-556:1.)

DFF259. Denied. Endo eliminated its entire sales force and stopped *promoting* Opana® as of January 2017. JTX-359-0003; Tr.556:2-12. That it

continued to sell Opana as of 2018 is irrelevant. Endo stopped the promotion of opioids as of January 2017.

> Defendants Finding No. 260. Dr. Fine and his colleagues do not prescribe BELBUCA because there are hosts of other drugs, including other opioids, which are sufficient for their patients. These include the opioids morphine, oxymorphone, oxycodone, hydromorphone, methadone, hydrocodone, fentanyl, Tramadol and Tapentadol. (Tr. 491:2-491:16.)

DFF260. Denied. Dr. Fine and his colleagues do not prescribe BELBUCA because they continue to underestimate the dangers of schedule II opioids. Tr.493:21-494:22, 868:20-869:8, 489:14-490:8, 870:24-872:21.

> Defendants Finding No. 261. Dr. Rauck has been retained as a consultant by BDSI independent of his work on this case. (Tr. 898:17-20.) Dr. Rauck helped design and implement the BELBUCA clinical trials. (Tr. 900:20-23.) Dr. Rauck is also a member of the Speakers' Bureau for BDSI to market drugs to other doctors. (Tr. 900:24-901:13.) BDSI hired Dr. Rauck to promote BELBUCA. (Tr. 901:14-20.) In connection with his role as a consultant for BDSI, Dr. Rauck has received confidential information that he could not share with competitors. (Tr. 900:16-19.) BDSI provides materials for Dr. Rauck's presentations when he has acts on their behalf, and BDSI pays Dr. Rauck when he acts as a speaker on their behalf. (Tr. 902:20-903:1.)

DFF261. Denied. Dr. Rauck is a clinician, not a marketer. He does not "market" BELBUCA or any other product, he educates doctors on the drug, presenting data and reports from clinical studies. Tr.901:2-902:13, 903:2-6. Given his expertise and reputation, many competing companies seek his assistance concerning clinical trials, which are confidential. Dr. Rauck abides by the

agreements and does not provide confidential material to one competitor about the other. (Tr.899:2-900:19.)

> Defendants Finding No. 262. Dr. Rauck prescribes opioids to 70 to 80% of his patients. (Tr. 905:2-905:4.) Of those patients on opioids, Dr. Rauck prescribes BELBUCA 25% of the time, and other opioids 75% of the time. (Tr. 905:5-905:11.) Up to half of all of Dr. Rauck's patients are prescribed Schedule II drugs. (Tr. 905:15-18.) Dr. Rauck currently prescribes fentanyl, hydromorphone, oxymorphone, morphine, oxycodone, and hydrocodone for the treatment of chronic pain. (Tr. 907:15-908:7.) Dr. Rauck testified that, while he still writes Schedule II prescriptions, "I many times wish I didn't write as much as I even do." (Tr. 926:14-18.) Dr. Rauck testified that "[w]e certainly have patients though that either pain condition has required the Schedule IIs or we cannot get them to transition over." (Tr. 908:18-20.)

DFF262. Denied. This finding constitutes excerpts of Dr. Rauck's testimony out of context and does not accurately represent his testimony at trial concerning his prescribing practices and the benefit of BELBUCA. Tr. 925:21-926:25; *see* PFF105-114. Dr. Rauck also published on successfully transitioning patients from schedule II drugs to BELBUCA. (Tr.908:11-17.)

> Defendants Finding No. 263. Buprenorphine is currently classified as a Schedule III opioid rather than Schedule II. However, for the treatment of chronic pain patients with opioids, there is no relevant difference between the two classifications because in either case, current regulatory standards, current standards of care, and the patient's best interest impose a duty to see patients face to face on a recurrent basis. (Tr. 488:20-490:8.)

DFF263. Denied. The DEA requires more restrictions on schedule II drugs because of their potential for abuse. Additionally, schedule II drugs have an increased risk of respiratory depression, which can be fatal. (Tr.870:23-872:21.) Dr. Rauck testified that safety influences his decision to prescribe BELBUCA over

a schedule II drug. BELBUCA is "safer in several aspects" than schedule II drugs and is effective at treating chronic pain. Tr.925:21-926:12; *see* PFF105-114.

> Defendants Finding No. 264. According to Endo, the DEA scheduling of BELBUCA ranked among the least relevant factors in terms of driving prescription behavior. (Tr. 466:16-467:10; DTX-043-0001.)

DFF264. Denied. This document appears to be dated sometime in 2016, at which point, BELBUCA has been on the market for less than a year. This document does not reflect the advantages of Schedule III drugs. *See* PFF111.

> Defendants Finding No. 265. The adverse events for BELBUCA are very typical for an opioid. (Tr. 501:25-503:13.)

DFF265. Denied. PFF105-114.

> Defendants Finding No. 266. The characteristics of BELBUCA with respect to respiratory depression and the ceiling effect were not surprising. (Tr. 501:16-20.)

DFF266. Denied. PFF105-114. Ongoing studies demonstrate that BELBUCA has very little to no respiratory depression, which is very different than other marketed opioids. Tr.880:23-881:12, 884:24-886:13, 887:16-889:16, 890:2-23; PTX-1060-0001; PTX-1059-0001; JTX-473-0007-0010.

> Defendants Finding No. 267. Dr. Fine is aware of no examples of industry praise from doctors that were not being paid by BDSI. (Tr. 511:3-6.)

DFF267. Denied. Plaintiffs do not understand what is meant "by paid by BDSI." Dr. Rauck is compensated for his time as a consultant.

> Defendants Finding No. 268. Vasisht I discloses all of the elements of claims 3-5 and 10 of the '866 patent, and claims 8 and 20 of the '843 patent. (D.I. 249 at 3; Tr. 232:2-232:13; 238:4-246:15; DDX3.36-DDX3.38)

DFF268. Admitted.

Defendants Finding No. 269. Paragraph [0063] of U.S. Application No. 11/817,915 (the U.S. National phase based on Vasisht I, filed January 21, 2010) discloses the following values and ranges for the pH of the polymeric diffusion environment for use with buprenorphine: (a) between about 4.0 and about 7.5; (b) about 6.0; (c) about 5.5 to about 6.5; (d) between about 6.0 and 6.5; (e) about 7.25; (f) between about 7.0 and 7.5; and (d) between about 7.25 and 7.5. (DTX-017 at [0063].) Dr. Michniak-Kohn testified that none of these values or ranges would suggest to a POSA that the patents disclose a pH between about 4 and about 6, between about 4.5 and 5.5 or between about 4.5 and 5 as recited in the claims. (DTX-206-0011 at [0063], Tr. 233:12-234:9.)

DFF269. Deny. See PFFs 115-126.

PFF115. Dr. Michniak-Kohn testified that paragraph 60 of the Vasisht-I application describes the pH ranges claimed in the '866 and '843 patents in support of her argument that Vasisht-I anticipates the claims of the '866 patent and '843 patents.

PFF116. Vasisht-I, however, is the same application as the '915 application and shares the same specification. (Tr.292:19-293:10.) Vasisht-I is PCT application PCT/US2007/016634. (DTX-017-0001-line 21, 0018.) The '915 application is the same application, PCT/US2007/016634. DTX-206-0001, line 86. The paragraphs in Vashisht-I (DTX-017) and the '915 application (DTX-206) are numbered slightly different. For this reason, paragraph 60 of Vasisht-I, for example, is identical to paragraph 63 of the '915 application.

Dr. Michniak-Kohn thus contradicts herself by arguing that the same application dose not describe the pH ranges for priority but does describe the pH limitations for anticipation

PFF117. The ’915 application does describe the pH ranges claimed in the ’866 and ’843 patents stating that the pH of the mucoadhesive polymeric diffusion environment may be “between about 4.0 and about 7.5”, “about 6.0”, and “that all values and ranges between these values and ranges are meant to be encompassed by the present invention.” (DTX-206, ¶63.) This language supports the claimed ranges. (Tr.656:1-657:5.)

PFF118. Further, ¶63 states that “the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof.” (DTX-206, ¶63.) A POSA would understand that the inventors were using the “pH of the device” as a shorthand for “the pH of the mucoadhesive layer of the device” in this sentence. (Tr.656:24-657:21; 659:13-17.)

PFF119. The ’915 application only discloses adjusting and measuring the pH of the polymeric diffusion environment of the mucoadhesive layer. (Tr.657:11-21.) There is no discussion of measuring the pH of the device as a whole or the backing layer. (*Id.*)

PFF120. The entirety of ¶63 refers to the pH of various "embodiments" of the mucoadhesive polymeric diffusion environment. (DTX 206, ¶63.) And the discussion is in a section of the patent discussing the polymeric diffusion environment, as shown by preceding and later paragraphs. (Tr 657:22-658:7; DTX 206, ¶¶ 62-67.)

PFF121. Example 1 of the '915 application teaches making three batches of the mucoadhesive layer and adjusting their pH values to 6, 7.25, and 8.5. (DTX-206, ¶103; Tr.658:8-24.) Devices with mucoadhesive layers having these pH values are later referred to in the '915 application as a "device at pH 6," "a device at pH 7.25," and "a device at pH 8.5." (Tr.658:25-659:17.) These pH values are referring to the pH of the mucoadhesive layers, and the "device at pH 6" is a shorthand abbreviation. (Tr.659:13-17.) The sentence in ¶63 was using "pH of the device" in the very same way.

PFF122. Similarly, the asserted claims of the '866 and '843 patents are also supported by the '726 application, which is an earlier application filed on July 21, 2006. (Tr.659:24-662:20; JTX-238.)

PFF123. The '726 application describes that "the device comprises a mucoadhesive layer comprising buprenorphine and having a pH between about 4 and about 7.5." (JTX-238, ¶18.)

PFF124. The '726 application also states, as a shorthand abbreviation, that "the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof. (JTX238, ¶20; Tr.660:9-18.)

PFF125. The abstract and the preceding paragraphs make clear that the application is only discussing measuring the pH of the mucoadhesive layer. (JTX-238-0024, ¶¶ 2, 18, 23; Tr.660:19-661:12.)

PFF126. The '726 application only teaches measuring the pH of the mucoadhesive layer and has an example that only adjusts and measures the pH of the mucoadhesive layer. (Tr.661:13-662:20; JTX-238, ¶62.)

Defendants Finding No. 270. The last sentence of paragraph [0063] of the '915 application states "[i]n other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0 or 7.5, or any incremental value thereof." Dr. Michniak-Kohn testified that a POSA would not have understood this sentence to refer to the pH of the polymeric diffusion environment; rather a POSA would have understood it to refer to the pH of the pharmaceutical dosage form ("the device" in the parlance of the asserted claims) as whole. (DTX-206-0011 at [0063], Tr. 235:13-238:3.)

DFF270. Denied. *See* PFF115-126.

Defendants Finding No. 271. "The device" is a term that appears in all of the asserted claims of the '866 and '843 patents and is used repeatedly in the specification of the '915 application, e.g., in the Abstract, paragraph [0004] of the Brief Summary of the Invention and in paragraph [0091] of the Detailed Description of the Invention. In each case, the term "the device" refers to the entire pharmaceutical dosage form and is distinct from the "polymeric diffusion environment" which comprises but one element of "the device." (DTX-206 at Abstract, [0004], [0091].)

DFF271. Denied. *See* PFF115-126.

Defendants Finding No. 272. The Abstract and ¶[0020] of Provisional Application 60/832,726 (to which the '915 application claims priority) is entirely consistent with that of the '915 application. The Abstract states that the pH of the mucoadhesive layer is between about 4 and about 7.5 and ¶[0020] only mentions the pH of "the device." (JTX-238-0009 at Abstract, ¶[0020].)

DFF272. Denied. *See* PFF115-126.

Defendants Finding No. 273. The demonstrative below, admitted into evidence (*see* Tr. 245:20-246:17) summarizes claims 3 and 10 of the '866 patent as compared to Vasisht I.

DFF273. Admitted.

Defendants Finding No. 274. The demonstrative below, admitted into evidence (*see* Tr. 245:20-246:17), summarizes claims 4 and 5 of the '866 patent as compared to Vasisht.

DFF274. Admitted.

Defendants Finding No. 275. The demonstrative below, admitted into evidence (*see* Tr. 245:20-246:17), summarizes claims 8-20 of the '843 patent as compared to Vasisht.

DFF275. Admitted.

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May 26, 2021

CERTIFICATE OF COMPLIANCE

I hereby certify that the text of the foregoing document uses a 14-point Times New Roman typeface and contains 12,054 words as determined by the word count feature of Microsoft Word (excluding the caption, tables, and signature block).

Date: May 26, 2021

/s/ Jeremy A. Tigan

Jeremy A. Tigan (#5239)

CERTIFICATE OF SERVICE

I hereby certify that on May 26, 2021, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on May 26, 2021, upon the following in the manner indicated:

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